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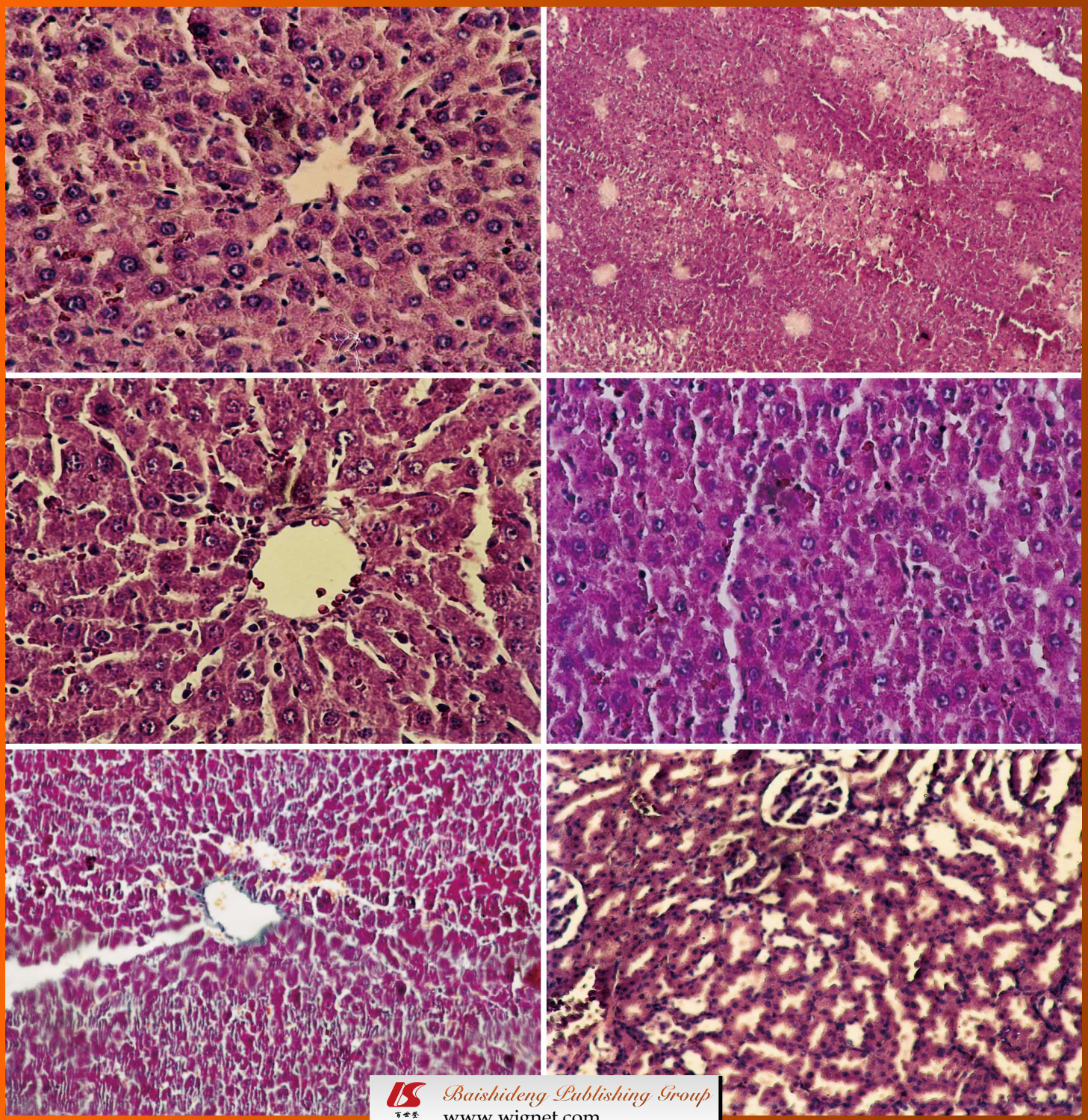

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Beijing 100025, China
Telephone: 0086-10-8538-1892
Fax: 0086-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

EDITING
Editorial Board of *World Journal of Gastrointestinal Pharmacology and Therapeutics,*
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-8538-1891
Fax: 0086-10-8538-1893
E-mail: wjgpt@wjgnet.com
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Fax: 00852-3115-8812
Telephone: 00852-5804-2046
E-mail: baishideng@wjgnet.com
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SUBSCRIPTION
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Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
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Jin-Lei Wang, Director
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No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-8538-1891
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ORIGINAL ARTICLE

Protective role of *Juniperus phoenicea* and *Cupressus sempervirens* against CCl_4

Sanaa Ahmed Ali, Maha Zaki Rizk, Nabawia Ali Ibrahim, Mohga Shafik Abdallah, Hayat Mohamed Sharara, Magda Mohamed Moustafa

Sanaa Ahmed Ali, Maha Zaki Rizk, Magda Mohamed Moustafa, Department of Theraputical Chemistry, National Research Centre, El-Behooth Street, 12622 Dokki, Giza, Egypt
Nabawia Ali Ibrahim, Department of Pharmacognosy, National Research Centre, 12622 Dokki, Giza, Egypt
Mohga Shafik Abdallah, Hayat Mohamed Sharara, Department of Chemistry, Faculty of Science, Helwan University, Ein Helwan, 11790, Helwan, Egypt
Author contributions: All the authors contributed to this manuscript.
Correspondence to: Sanaa Ahmed Ali, Assistant Professor, Department of Therapeutic Chemistry, National Research Centre, El-Behooth Street, 12622 Dokki, Giza, Egypt. sanaa_ahmedibrahim@yahoo.com
Telephone: +20-2-33371433 Fax: +20-2-33370931
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Abstract

AIM: To investigate the role of *Cupressus sempervirens* (*C. sempervirens*) and *Juniperus phoenicea* (*J. phoenicea*) extracts as therapeutic effect against CCl_4 with biochemical, histopathological evaluations.

METHODS: A single intraperitoneal dose of 10% CCl_4 in olive oil (1 mL/kg body weight) was administered to a group of female Wister rats, sacrificed after 24 h (as the injury group). The other groups were given CCl_4 as described above and divided as follows: two groups of ten rats each were orally administered either *J. phoenicea* extract or *C. sempervirens* extract three times per week for six weeks and a further group administered CCl_4 was left for six weeks to allow self-recovery. At the end of experiment, the rats from all groups were sacrificed for sampling and for biochemical and histological analysis.

RESULTS: Remarkable disturbances were observed in the levels of all tested parameters. On the other hand, rats injected with the toxic agent and left for one and a half month to self recover showed moderate improvements in the studied parameters while, treatment with both medicinal herbal extracts ameliorated the levels of the disturbed biochemical parameters. The group treated with *J. phoenicea* extract showed a remarkable improvement in comparison to the CCl_4 treated group. The *C. sempervirens* group revealing an even more remarkable effect showing histopathological liver& kidney profiles close to those of the control group.

CONCLUSION: *C. sempervirens* and *J. phoenicea* leaf extracts show a remarkable effect in enhancing liver and kidney functions and may thus be of therapeutic potential in treatment hepatotoxicity and nephrotoxicity.

Key words: *Cupressus sempervirens*; *Juniperus phoenicea*; Carbon tetrachloride; Hepatotoxicity; Nephrotoxicity

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INTRODUCTION

Alternative drugs for treatment of liver and kidney disease have become a necessity to replace currently used drugs of doubtful efficacy and safety. Thus there is a world-wide

trend to return to traditional medicinal plants to treat liver ailments[1]. Anti-fibrotics from natural products used in traditional medicine may reduce the risk of toxicity and maintain the therapeutic effectiveness when the drug is used clinically[2,3]. The use of natural products as a means for treatment and protection against diseases may be effective, less toxic and also less costly. The aim of the present study was to determine the potential role of the two plants extracts *Juniperus phoenicea* (*J. phoenicea*) and *Cupressus sempervirens* (*C. sempervirens*) in preventing or ameliorating the deleterious effects induced by experimental chemical hepatotoxins. In a previous study on the hepatoprotective effects of these two extracts, various biochemical determinants of liver function were evaluated including L-alanine aminotransaminase, aspartate aminotransaminase, and alkaline phosphatase, hight density lipoprotein low density lipoprotein, bilirubin, total cholesterol and triglycerides. Certain antioxidants were also measured, namely, glutathione, lipid peroxides and nitric oxide[4] and the study showed that treatment with both extracts ameliorated the levels of the disturbed biochemical parameters.

In this study we aimed to study the therapeutic effect of both extracts (*J. phoenicea* and *C. sempervirens*) against CCl_4-induced hepatotoxicity in rats. This was achieved by measuring liver total protein and albumin. Serum total lactate dehydrogenase (LDH) was also measured and LDH-isoenzymes were analysed electrophoretically. Kidney functions were measured as serum urea and creatinine to evaluate the protective effect of both extracts against chemical toxicity. The histopathology of the architecture of liver and kidney was also investigated to investigate the role of the studied extracts on the architecture of injured liver and kidney cells.

MATERIALS AND METHODS

Chemicals

All chemicals used in the present study were of high analytical grade products from Sigma, Aldrich (St. Louis, MO, USA), Merck (Germany), BDH (England), Riedal de Ha'en (Germany), Fluka (Switzerland), Randox (United Kingdom), and Bio-diagnostic (Egypt).

Animals

Adult female albino Wister rats weighing approximate 120 g, supplied from the animal house of National Research Center, Dokki, Egypt were used for experimental investigations. Animals were kept under constant environmental and nutritional conditions and were given food and water all throughout the period of the experiment. Appropriate anaesthetic and sacrifice procedures were followed ensuring that animals did not suffer at any stage of the experiments. Anaesthetic procedures complied with the legal ethical guidelines approved by the Ethical Committee of the Federal Legislation and National Institutes of Health Guidelines in USA and were approved by the ethical committee of the National Research Centre in Egypt. Animals were sacrificed under mild ether anesthesia. Blood was withdrawn and serum separated then liver and kidney samples were collected.

Extraction of the powdered leaves

The dried powdered leaves (500 g) of either *Juniperus phoenicea* L. or *Cupressus sempervirens* L. were extracted in a Soxhlet apparatus with methyl alcohol. The methanolic extract was evaporated to dryness. The dried methanolic extract (approximate 28 g) was dissolved in a suitable amount of hot distilled H_2O- MeOH (95:5 v/v, 200 mL) and partitioned between ethyl acetate and methanol. The ethyl acetate extract was partitioned between $CHCl_3$ and EtOAc. Separation was then carried out by silica gel thin layer chromatography plates using solvent system C_6H_6-C_5H_5N-HCOOH. The isolated compounds were purified on Sephadex LH_{20} and were eluted with MeOH giving two major biflavonoid compounds from both plants. The methanolic fractions were chromatographed over Sephadex LH_{20} CC, eluted with H_2O and finally with 50% MeOH. Five flavonoids were isolated from *Cupressus sempervirens* L. and four from *Juniperus phoenicea* L., while two phenolic acids were isolated from both plants. The isolated compounds were purified by paper chromatography using solvent system BuOH- Ac0H- H_2O (4:1:5 v/v/v) upper layer. The isolation procedures for both plants were performed in Department of Pharmacognosy, National Research Centre, Dokki, and Giza, Egypt.

Experimental design

Fifty adult female albino Wister rats were divided into five groups of ten rats each. The first untreated group served as control (Group 1). The second group which served as the cirrhotic control group received a single intraperitoneal (i.p) injection of 1 mL/kg body weight 10% CCl_4 in olive oil), and was then sacrificed after 24 h and (Group 2)[5]. The remaining three groups were given CCl_4 as described before and divided as follows: Group 3 - CCl_4 treated rats, left for one and half months to self-recover; Group 4 - CCl_4-treated rats administered *J. phoenicea* methanolic extract (E1) (300 mg/kg body weight) three times per weeks orally for one and half months; and Group 5 - CCl_4-treated rats administered *C. sempervirens* methanolic extract (E2) (300 mg/kg body weight) three times per week orally for one and half months.

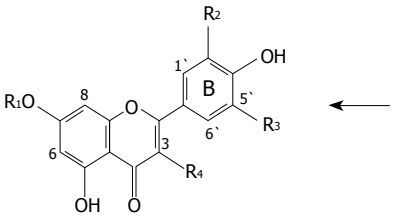
Preparation of samples

At the end of experiment, animals were fasted for 24 h, and blood was then withdrawn from the sublingual vein after anesthetizing with diethyl ether. Blood samples were centrifuged for ten minutes at 3000 r/min, and then serum was separated and stored in aliquots in eppendorf tubes at -20℃ to be used for biochemical analyses.

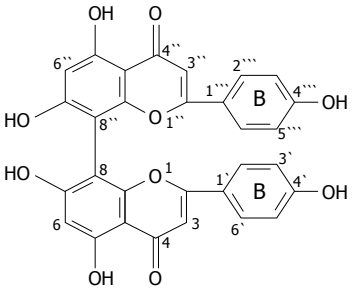
Animals were then sacrificed, liver and kidney tissues was rapidly removed and cut into small sections which were put in 10% of formalin solution and left for histopathological analysis. Collected serum samples were subjected to the analytical methods.

Analytical determinations

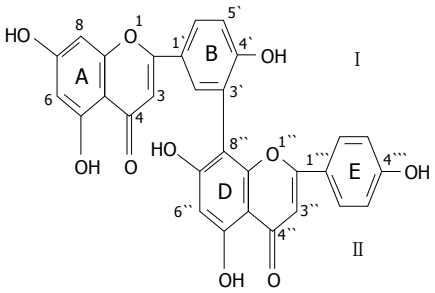
Total proteins: Total protein reacts with Bradford reagent to give a blue complex, which is measured colorimetrically at 595 nm wavelength[6].



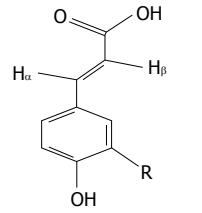
Compounds	R_1	R_2	R_3	R_4
Rutin[1]	H	OH	H	*O*-glucorhamnosyl
Myricitrin	H	OH	OH	*O*-rhamnosyl
Quercetin	H	OH	H	OH
Cosmosiin	*O*-glucosyl	H	H	H
Quercitrin	H	OH	H	*O*-rhamnosyl



Amentoflavone



Cupressuflavone



R = H ρ-Coumaric acid

R = OH Caffeic acid

Figure 1 Chemical composition of the methanolic extracts of *Cupressus sempervirens* L. or *Juniperus phoenicea* L.except Rutin present in *Cupressus sempervirens* L. only. [1]Rutin present in *Cupressus sempervirens* leaves only and revealing a more remarkable effect in histological studies of liver and kidney.

Determination of albumin level: This was performed according to Doumas *et al*[7] using Randox Diagnostic kits. In a buffered solution, bromocresel green forms a green colored complex with albumin the intensity of which is proportional to the amount of albumin present in the sample.

Determination of serum urea level: This was done according to the procedure of Patton and Crouch[8] using Diamond International Kits. In alkaline medium, the ammonium ions released by urease react with salicylate and hypochloride to form green indophenols. The absorbance of samples and standards were measured by spectrophotometer at 580 nm against a reagent blank. The concentration of urea (mg/dL) was determined.

Determination of serum creatinine level: This was done according to the procedure of Henry[9]. The rate of complex formation was measured photometrically at 492 nm, and the concentration of serum creatinine was measured as mg/dL.

Determination of LDH activity in serum: LDH activity was estimated by the method of Babson and Babson[10]. The reduction of NAD is coupled with the reaction of tetrazolium salt as Iodonitrotetrazolium chloride (INT) with phenazine methosulfate serving as an intermediateelectron carrier, resulting in the formation of formazan of INT. The developed color was measured at 503 nm and the activity was calculated as μmol/min per mg protein.

Electrophoretic separation of serum LDH-isoenzymes: The method of Dietz and Lubrano[11] was adopted for the preparation of ultra-thin layers of 5.5% polyacrylamide gel, for separation of LDH isoenzymes. The dry gel handles like a piece of paper[12] and can be stored for a long time without fading, distortion or cracking. The dry gel was scanned at 575 nm with an Ultrascan Laser Densitometer.

Histopathological analysis: Small pieces liver and kidney from the experimental animals were fixed in 10% neutral buffered-formalin prior to routine processing in paraffin-embedded blocks. Sections (4 μm thick) were cut and stained using hematoxylin-eosin (HE)[13].

Statistical analysis: All data obtained are expressed as the mean ± SD. Results were analyzed by a computerized statistical program. Values were compared by one-way analysis of variance and Fisher's protected least significance difference for multiple comparisons as the *post hoc* test. A *P*-value < 0.05 was considered to be statistically significant[14].

RESULTS

Chemical composition

Chemical composition of the methanolic extracts of *Cupressus sempervirens* L. or *Juniperus phoenicea* L. was investigated by column chromatography followed by thin layer and paper chromatography. This revealed the presence of two major biflavonoid compounds; cupressuflavone and amentoflavone in the EtOAc fraction. Four flavonoid compounds namely, myricitrin, quercetin, cosmosin, quercitrin and two phenolic compounds; ρ-coumaric acid and caffeic acid were isolated from MeOH fraction of *Juniperus phoenicea* L. A further flavonoid, rutin was also identified in *Cupressus sempervirens* (Figure 1). Each isolated compound was identified by ^{1}HMR and ^{13}C-NMR spectral analysis[15].

Serum biochemical parameters

Serum total protein showed a pronounced decrease in the

Table 1 Effect of *Juniperus phoenicea* and *Cupressus sempervirens* leaves on the levels of some biochemical parameters in CCl_4-toxicated serum of rats

Parameters	Control	CCl_4-toxicated	CCl_4-self recovery	Treated groups		Improvement (%)			ANOVA (*P*)
				Ext_1	Ext_2				
	G_1	G_2	G_3	G_4	G_5	G_3	G_4	G_5	
Total protein (TP)	7.28 ± 0.61 (2)	5.458 ± 0.55 (1,3,4,5)	6.95 ± 0.28 (2)	6.94 ± 0.43 (2)	7.18 ± 0.42 (2)	20.5	20.83	23.7	< 0.0001
Albumin (Alb)	2.86 ± 0.45 (NS)	2.64 ± 0.11 (NS)	2.69 ± 0.12 (NS)	2.73 ± 0.31 (NS)	2.84 ± 0.24 (NS)	1.74	3.41	7.0	< 0.348
Urea	0.606 ± 0.071 (2)	0.9809 ± 0.15 (1,3,4,5)	0.620 ± 0.053 (2)	0.619 ± 0.1102 (2)	0.613 ± 0.0759 (2)	59.6	59.7	59.7	< 0.0001
Creatinine	0.293 ± 0.079 (2)	0.480 ± 0.08 (1,3,4,5)	0.338 ± 0.07 (2)	0.353 ± 0.021 (2)	0.294 ± 0.065 (2)	48.7	52.73	63.6	< 0.0001
Activity (LDH)	0.098 ± 0.028 (2)	0.495 ± 0.242 (1,3,4,5)	0.1237 ± 0.019 (2)	0.104 ± 0.0412 (2)	0.100 ± 0.017 (2)	479.6	499.59	503.8	< 0.0001

Data are expressed as mean ± SD of ten rats in each group. Values of total protein are expressed as g/dL and Albumin are expressed as g/L; Urea and Creatinine are expressed as mg/dL; Lactate dehydrogenase (LDH) are expressed as U/mL. *P* is level of significance, where P < 0.0001 is significant. Analysis of data is carried out by one way (ANOVA) (analysis of variance) accompanied by *post hoc* (LSD) (least significant difference) (SPSS computer programme). Ext_1 means CCl_4 + Me-OH extract of *Juniperus phoenicea* leaves and Ext_2 means CCl_4 + Me-OH extract of *Cupressus sempervirens*. NS: Not significant.

Table 2 Effect of *Juniperus phoenicea* and *Cupressus sempervirens* leaves on the level of lactate dehydrogenase isoenzymes of CCl_4-toxicated serum of rats

Parameters	Control	CCl_4-toxicated	CCl_4-self recovery	Treated groups		Improvement (%)			ANOVA (*P*)
				Ext_1	Ext_2				
	G_1	G_2	G_3	G_4	G_5	G_3	G_4	G_5	
LDH_1	0.0036 ± 0.0009 (2)	0.0193 ± 0.017 (1,3,4,5)	0.00767 ± 0.0028 (2)	0.00775 ± 0.0052 (2)	0.00904 ± 0.0056 (2)	324.86	322.63	286.596	< 0.037
LDH_2	0.012 ± 0.004 (2)	0.0279 ± 0.0179 (1,5)	0.0165 ± 0.0039 (NS)	0.0161 ± 0.0131 (NS)	0.0086 ± 0.006 (2)	96.61	100	163.56	< 0.044
LDH_3	0.0131 ± 0.0075 (NS)	0.0199 ± 0.010 (3,4,5)	0.0100 ± 0.0025 (2)	0.0106 ± 0.0094 (2)	0.00727 ± 0.0014 (2)	75.57	70.99	96.41	< 0.057
LDH_4	0.00813 ± 0.00479 (2)	0.0411 ± 0.0314 (1,3,4,5)	0.0106 ± 0.0035 (2)	0.0102 ± 0.0063 (2)	0.0123 ± 0.0054 (2)	375.15	380.07	354.24	< 0.003
LDH_5	0.0673 ± 0.0186 (2)	0.409 ± 0.217 (1,3,4,5)	0.0866 ± 0.0189 (2)	0.081 ± 0.008 (2)	0.066 ± 0.019 (2)	479.02	487.19	510.37	< 0.0001

Data are expressed as mean ± SD of ten rats in each group. Values of lactate dehydrogenase isoenzyme (LDH_1) are expressed as U/mL. *P* is level of significance, where *P* < 0.0001 is significant. Analysis of data is carried out by one way (ANOVA) (analysis of variance) accompanied by *post hoc* (LSD) (least significant difference) (SPSS computer programme). Ext_1 means CCl_4 + Me-OH extract of *Juniperus phoenicea* leaves and Ext_2 means CCl_4 +Me-OH extract of *Cupressus sempervirens*. NS: Not significant.

CCl_4-intoxicated group, with a reduction of 25% compared to the normal healthy control group. Groups 3, 4 and 5 showed an improvement in the level of total protein amounting to 21%, 21% and 24% respectively compared to the CCl_4-intoxicated group (G_2). Concomitantly, a slight improvement was found in the level of serum albumin of 2%, 3% and 7% for groups 3, 4 and 5 respectively, compared to the CCl_4-toxicated group (G_2). The level of serum urea was significantly increased (62%) in the CCl_4-toxicated group (G_2) compared to the control healthy group. Administration of *J. phenociea* or *C. sempervirens* to the CCl_4-toxicated group (G_4 and G_5 respectively) or without any treatment (G_3) still showed a slight significant increase in urea level (2%, 3% and 2%) for groups G_4, G_5 and G_3 respectively compared to the control healthy group. In addition, serum creatinine and total LDH activities were significantly increased in group 2 compared to the control group. Treatment with the two extracts showed a significant decrease in the levels of creatinine compared with the CCl_4-intoxicated group (G2) with a percentage change of 15%, 11% in G_4, G_5 respectively (Table 1 and Figure 2A).

Electrophoretic profiles of LDH-isoenzymes

The levels of LDH_1 was greatly increased in the CCl_4-intoxicated group (G_2) with a percentage change of more than 439.11% compared to normal healthy control group, while G_3, G4 and G_5 showed a lowering in the levels of LDH_1 of 325%, 323% and 287% resp. LDH_2, LDH_3, LDH_4 and LDH_5 are also significantly increased in the CCl_4-intoxicated group compared to the control group. Treatment with the two extracts induced a highly significant decrease in the levels of the four isoenzymes, as illustrated in Table 2, Figure 2B and Figure 3.

Histological and histopathological observation in liver and kidney

Histologically, control livers stained with HE staining showed normal parenchyma architecture (Figure 4A). After CCl_4 treatment, significant liver damage was observed with classic histology of cirrhosis, coagulative necrosis, massive fibrosis, fatty degeneration and formation of regenerative nodules (Figure 4B). The group treated with *J. phoenicea* extract showed a remarkable improvement compared to the

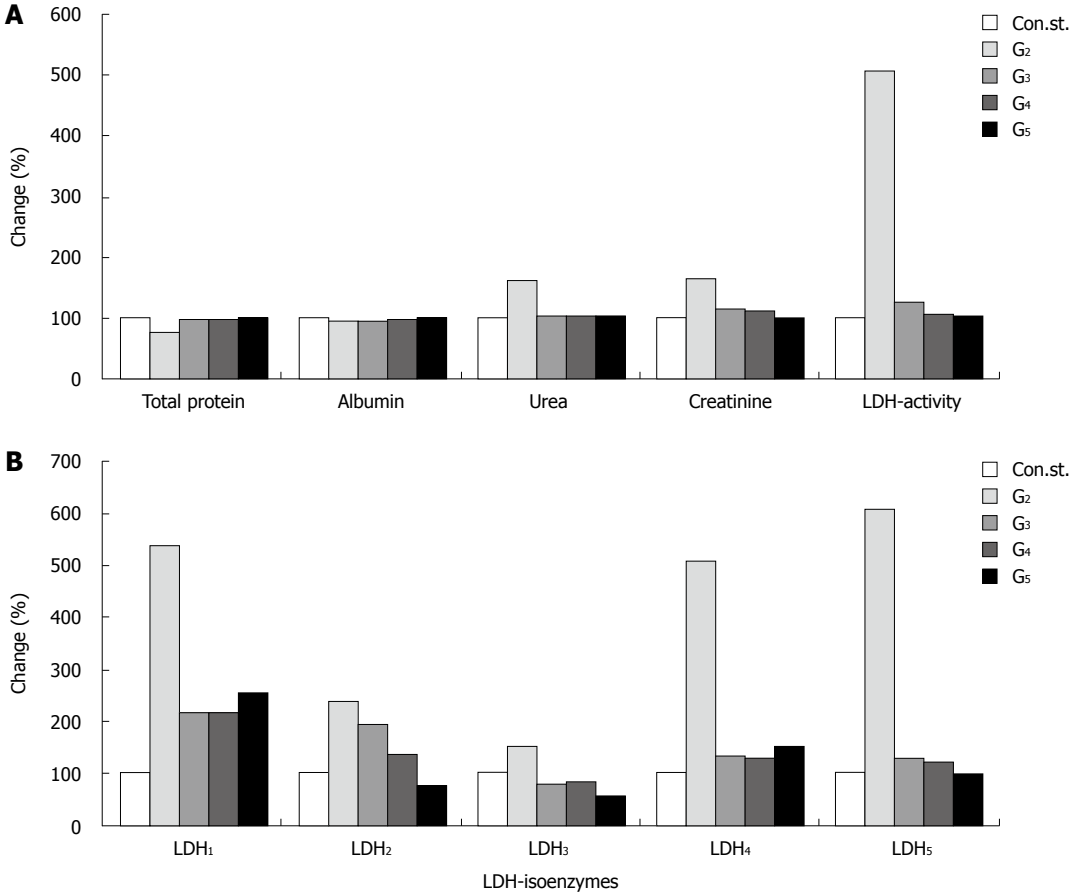


Figure 2 Diagrammatic representation illustrating the percentage change in total protein, albumin, urea, creatinine, lactate dehydrogenase-activity (A), and lactate dehydrogenase-isoenzymes (B) in rat serum of different groups as compared to control. LDH: Lactate dehydrogenase.

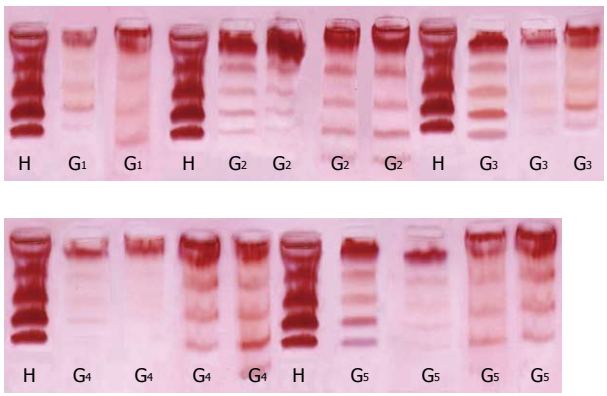


Figure 3 Electrophoretic profile of lactate dehydrogenase isoenzymes in heart (H), liver (L) of rats control group (G_1); CCl_4 group (G_2); CCl_4 (self-recovery) group (G_3); CCl_4 + *Juniperus phoenicea* group (G_4); CCl_4 + *Cupressus sempervirens* (G_5).

CCl_4-treated group (Figure 4C). The *C. sempervirens* group showed an even more remarkable effect with values close to those of the control group (Figure 4D). In the group of rats intoxicated with CCl_4 and left without further treatment for 6 wk to allow self-recovery, the liver parenchyma still showed massive fibrosis and micronodular cirrhosis as well as moderate fatty change and regenerative nodules surrounded by fibrous connective tissue extending between portal regions, similar to animals treated with CCl_4 (G_2) (Figure 4E). The regression in these alterations was slower than the groups treated with both extracts.

Microscopically, kidney stained with HE staining showed Glomeruli and tubules with apparently normal histological features (Figure 5A). However in the CCl_4 (24 h) group extensive cortical damage was observed (Figure 5B). Focal glomerular necrosis was detected in this group and the affected glomeruli showed hypocellularity and shrinkage. Most of the cortical tubules showed morphologic changes, some of them being dilated and lined with flattened epithelial cells. In the group of rats protected with *C. sempervirens* or *J. phoenicea* to CCl_4-toxicated group, the glomeruli were normal, although sparse tubular changes were observed. Treatment with *C. sempervirens* (Figure 5C) showed a more remarkable improvement than *J. phoenicea* (Figure 5D). In the group of rats intoxicated with CCl_4 and left for one and half month without any treatment to allow self-recovery (Figure 5E) the kidney glomeruli still showed a few necroses with some epithelial cells showing vacuolization, atrophy and detachment of tubular epithelial cells. The regression in theses alteration was slower than in the groups treated with both extracts.

DISCUSSION

In CCl_4-induced injury, the brunt of the damage falls on hepatocellular membranes. The relative loss of phospho-

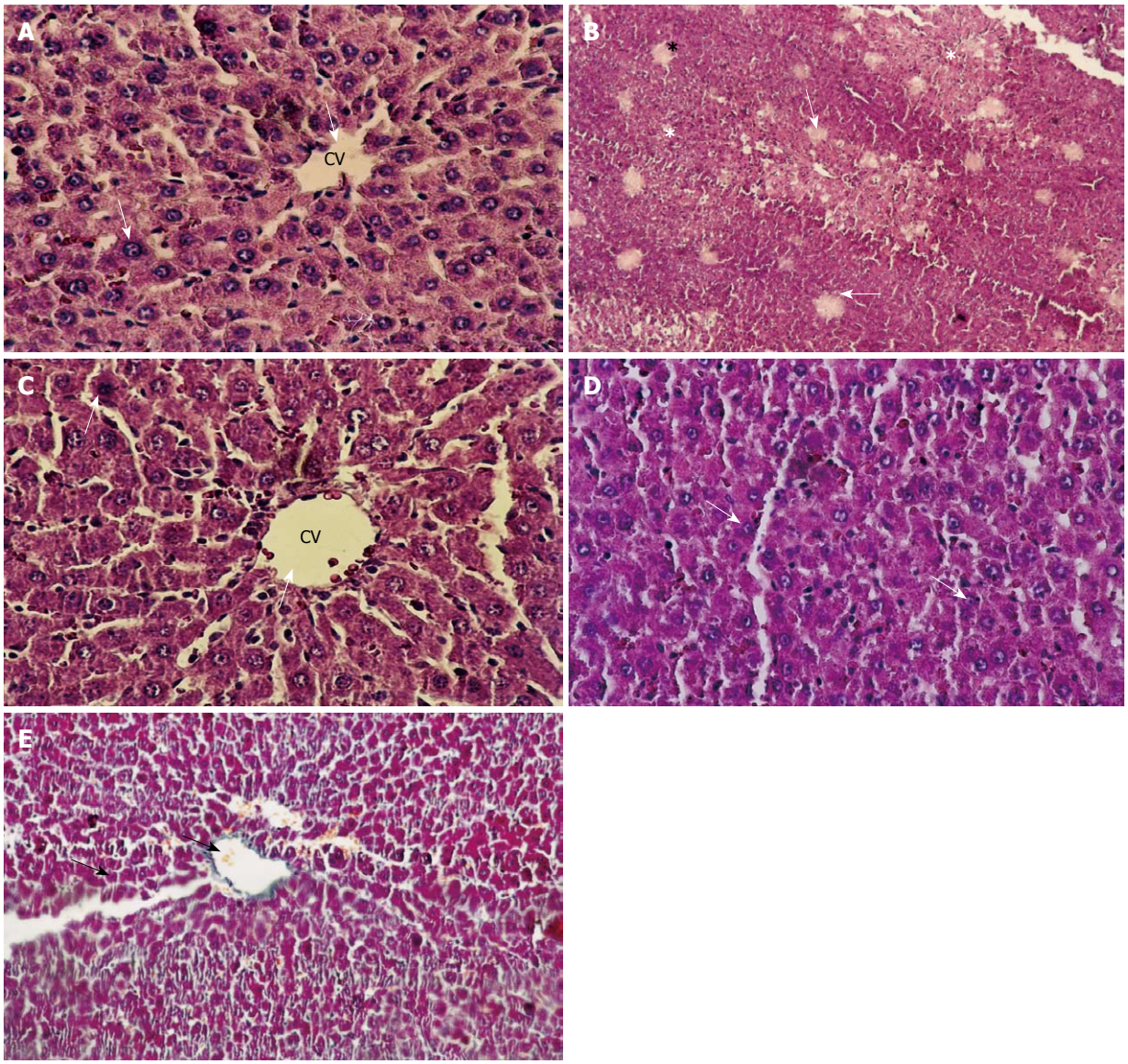


Figure 4 Histological appearance of the liver (HE staining). A: Section of control liver showing a normal histological appearance (arrows) (× 200); B: Liver section of a rat treated with CCl_4 (24 h) showing classic cirrhotic appearance (arrows) with the presence of coagulative necrosis (asterisks), note the necrosis of hepatic cells and formation of vacuoles (arrows) (× 100); C: Liver section of a rat treated with CCl_4 + *Cupressus sempervirens* group showing hepatocytes, with normal histological profile, arrows indicated (CV) normal hepatocyte (× 200); D: Liver section of a rat treated with CCl_4 + *Juniperus phoenicea* group, except for fatty degeneration (arrows), the lobular appearance is normal (× 100); E: Liver section of a rat treated with CCl_4 (1.5 mo self-recovery group) showing micronodular cirrhosis (arrows) is seen along with moderate fatty change. Note the regenerative nodule surrounded by fibrous connective tissue extending between portal regions (× 100). CV: Central vein

lipids moieties results in an alteration of the membrane cholesterol:phospholipids ratio leading to abnormal transmembrane losses of fluid, abnormal transmembrane signal transmission and ultimately to cell injury, fibrosis or death[16]. It should be pointed out that treatment of liver diseases by various synthetic drugs is costly and may induce undesirable side- effects. An alternative approach to the use of chemically synthesized drugs for the treatment of liver disorders is the use of natural plant extracts, some of which have been used by traditional medical practitioners for centuries. The potency of these extracts will open new areas for the development of a safe and cheap hepatoprotective drugs from natural sources for treatment of a wide range of liver diseases[17].

The phytochemical investigation of the methanolic extract of *J. phoenicea* and *C. sempervirens* revealed the presence of flavonoids and phenolic acids, which possess significant antioxidant and thereby anti-hepatotoxic properties[18]. Previously, the free radical scavenging properties against $DPPH^0$ of flavonoids from the two plants under investigation were measured using ESR techniques in comparison with α-tocopherol as standard antioxidant. A high antioxidant activity for quercetin, rutin, caffeic acid, and p-coumaric acid were reported[19]. Leaf extracts of *C. sempervirens* play an important role in traditional herbal medicine and are used as antiseptic, antirheumatic, antihemorrhoidal, antidiarrheic, vasoconstrictive agents, for cough, colds, parasitic infections, inflammation and as strong hair tonic. It is also used for treatment of gastrointestinal disorders (diarrhea) and against dermatosis[20,21].

Elevated serum levels of liver-specific enzymes as well as alterations in several other liver parameters and reduc-

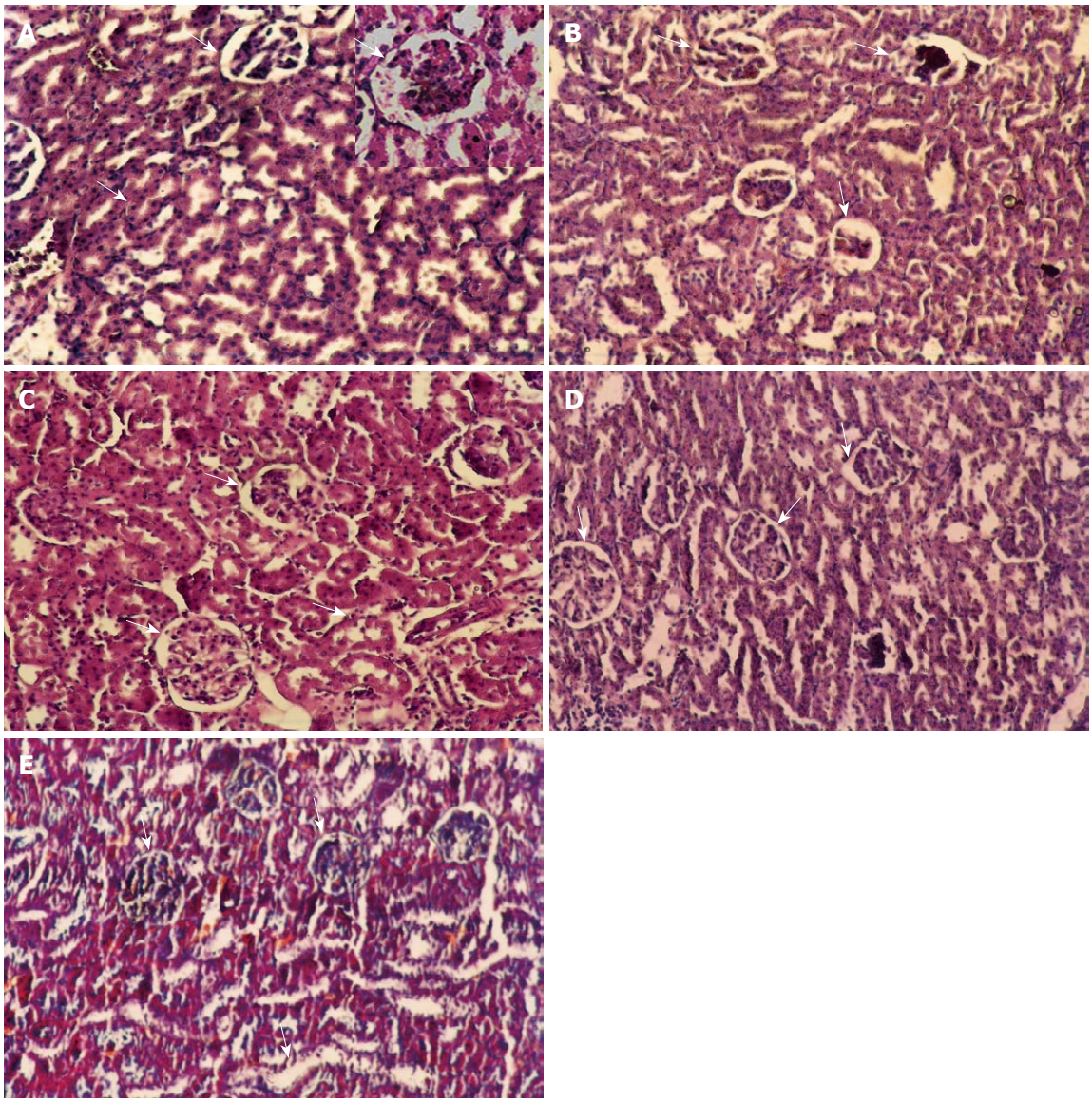


Figure 5 Histological appearance of the kidney (HE staining). A: Section of control kidney showing a normal histological appearance glomeruli and tubules (arrows) appear normal (× 100), with higher magnification section (× 200); B: Renal cortex in CCl_4 (24 h) group. Segmental glomerular necrosis (arrows) seen, tubular dilation (arrows) and detachment of tubular epithelial cells also visible (× 100); C: Renal cortex in CCl_4 + *Cupressus sempervirens* group, glomeruli and tubules (arrows) appear normal in cortex (× 200); D: Renal cortex in CCl_4 + *Juniperus phoenicea* group, glomeruli and tubules (arrows) appear normal seen in cortex (× 100); E: Renal cortex in CCl_4 group (1.5 mo, self-recovery) group. Vacuolization, atrophy and detachment of tubular epithelial cells (arrows) seen (× 100).

tion in the levels of serum total proteins may indicate liver or kidney disease[22]. The present data showed that rats treated with a single dose of CCl_4 developed significant hepatic damage as observed from the decreased level of total protein. The decline in protein content may be due to defects in protein biosynthesis as well as disruption and dissociation of polyribosomes from endoplasmic reticulum following administration of CCl_4[23]. The improvements in the level of total protein after treatment with the natural products may be due to the promotion of ribosome assembly on endoplasmic reticulum which facilitates uninterrupted protein biosynthesis[24]. In the present study, a significant reduction in serum albumin was detected in the CCl_4-intoxicated rats while a slight improvement occurred after treatment with the two test extracts. These results are in agreement with Ohta *et al*[25] who reported that, serum albumin concentrations decrease in rats with chronic CCl_4-intoxication at an advanced state of liver cirrhosis.

CCl_4-intoxicated rats showed a significant increase in the levels of serum urea and creatinine due to altered kidney function. This is in agreement with the findings of Ronis *et al*[26] who noted that administration of CCl_4 causes increases in plasma creatinine levels in rats. Administration of *J. phoenicea* or *C. sempervirens* extracts to cirrhotic rats induced a significant decrease in the levels of serum urea and creatinine in comparison to rats left to recover without any treatment.

LDH is a key enzyme in glycolysis which catalyzes the process of lactate production[27]. The results obtained in the present study revealed significant increases in the levels of total LDH in CCl_4-intoxicated rats. This correlates with the findings of Hung *et al*[28] who noted that exposure of

rats to CCl_4 increased the serum levels of LDH. However, treatment of cirrhotic rats with *J. phoenicea* or *C. sempervirens* extracts resulted in decreased levels of total LDH. Our results also coincide with those of Gupta *et al*[29] who noted a significant increase in serum levels of all LDH the isoenzymes. Analysis of each tissue revealed characteristic changes in LDH isoenzyme patterns indicating organ-specific tissue damage. These alterations in LDH and its isoenzymes, may be directly or indirectly related to the mechanism(s) of the toxic action, and also provide insight into the site/organ(s) of toxicity[29]. Levels of all LDH-isoenzymes were improved after treatment with both extracts. An excellent enhancement in LDH_5 was also noticed after treatment with the two extracts. It was clearly noticed that, as predominating isoenzymes, both LDH_4 and LDH_5 were more or less at normal levels.

Furthermore, CCl_4 treatment induces the necrosis of hepatocytes around centrilobular veins, and the accumulation of inflammatory cells[30,31]. In the present study, histopathological changes we observed indicating liver damage after CCl_4 administration. It has been reported that CCl_4 causes necrosis, fibrosis, steatosis and foamy degeneration of hepatocytes and cirrhosis in liver. It is worth noting that the present biochemical findings correlated with the histological observations in the liver and kidney which clearly revealed that the hepatic cells, central vein, and portal triad and kidney normal histologic features Glomeruli and tubules are almost normal in *J. phoenicea* L or *C. sempervirens* groups.

The result of this study, confirmed by histological observation, show that methanolic extracts from both plants under investigation have preventive action on CCl_4 induced hepatotoxicity. This phenomenon was due to flavonoid compounds namely myricitrin, quercetin, cosmosin and quercitrin as well as the phenolic compounds ρ-coumaric acid and caffeic acid. The role of these extracts in restoring different enzymatic activities and in ameliorating the toxic and hazardous disorders induced on the liver and kidney may be due to a high antioxidant activity for these flavonoids, especially rutin, which present in *C. sempervirens* leaves. The potency of the extracts will open new areas for the development of a safe and cheap hepatoprotective drug from natural wealth for the treatment of a wide range of liver diseases.

COMMENTS

Background

The methanolic extracts of the leaves of two traditional medicinal plants, namely, *Cupressus sempervirens* (*C. sempervirens*) and *Juniperus phoenicea* (*J. phoenicea*) were evaluated for their therapeutic effect.

Research frontiers

The phytochemical investigation of the methanolic extracts of *J. phoenicea* and *C. sempervirens* revealed the presence of flavonoids and phenolic acids, which possess significant antioxidant and thereby anti-hepatotoxic properties.

Innovations and breakthroughs

The flavonoid compounds, myricitrin, quercetin, cosmosin, quercitrin and the phenolic compounds ρ-coumaric acid and caffeic acid. The role of these extracts in restoring different enzymatic activities and in ameliorating the toxic and hazardous disorders induced on the liver and kidney.

Applications

The levels of serum biochemical parameters including total protein, albumin, total lactate dehydrogenase activity, lactate dehydrogenase isoenzymes were determined. In addition urea and creatinine were estimated as measures of kidney function in experimentally CCl_4 induced liver injury in rats. The histopathological liver and kidney profiles were also studied.

Peer review

The two extracts under study possess potent activities against CCl_4 toxicity due to the high antioxidant activity of the flavonoids, especially rutin, which are present in *C. sempervirens* leaves. The potency of the extracts will open new areas for the development of a safe and cheap hepatoprotective drug from natural wealth for the treatment of a wide range of liver diseases.

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CASE REPORT

Mesalamine induced symptom exacerbation of ulcerative colitis: Case report and brief discussion

Maneesh Kumar Gupta, Scott Pollack, John J Hutchings

Maneesh Kumar Gupta, Department of Internal Medicine, LSU Health Sciences Center, New Orleans, LA 70112, United States
Scott Pollack, Department of Medicine, Section of Gastroenterology and Hepatology, Tulane University Health Sciences Center, New Orleans, LA 70112, United States
John J Hutchings, Department of Medicine, Section of Gastroenterology and Hepatology, LSU Health Sciences Center, New Orleans, LA 70112, United States
Author contributions: Gupta MK and Pollack S researched the topic and wrote the case report and discussion; Hutchings JJ acutely treated this patient during her hospital stay and reviewed this paper, providing appropriate feedback.
Correspondence to: John J Hutchings, MD, Department of Medicine, Section of Gastroenterology and Hepatology, LSU Health Sciences Center, 1542 Tulane Avenue, Suite 423 Box T4M-2, New Orleans, LA 70112, United States. jhutc1@lsuhsc.edu
Telephone: +1-504-5684498 Fax: +1-504-5682127
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Abstract

This paper describes a rare case in which the oral administration of mesalamine resulted in the exacerbation of ulcerative colitis (UC) in a patient who was previously responsive to mesalamine and whose colitis had been in remission for eight years. Mesalamine and other 5-aminosalicylic acid compounds are the mainstay of treatment for UC; however up to 8% of patients are unable to take the medications due to intolerance or hypersensitivity reactions. Common drug reactions are fever, nausea, diarrhea and abdominal pain; however, exacerbation of UC has rarely been reported. This study highlights the importance of ruling out mesalamine as the causative agent in cases of UC exacerbations.

Key words: Mesalamine; Exacerbation; Ulcerative colitis; Inflammation; Adverse drug reaction

Peer reviewer: Ole Haagen Nielsen, Professor, Chief Physician, Department of Gastroenterology, Medical Section D112M, Herlev Hospital, University of Copenhagen, Herlev Ringvej 75, DK-2730 Herlev, Denmark

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INTRODUCTION

This paper describes a 28-year old woman with a history of ulcerative colitis (UC) who developed worsening of her bloody diarrhea and abdominal pain after the reintroduction of mesalamine therapy. The patient developed inflammatory changes of her colon similar to that which is seen in typical UC exacerbation. After the discontinuation of mesalamine, the patient's symptoms quickly subsided. Mesalamine is chemically very similar to sulfasalazine, one of the mainstays of UC therapy. Unlike sulfasalazine, mesalamine lacks a sulphapyridine moiety that has been implicated in many of the adverse reactions associated with sulfasalazine. This paper describes the proposed mechanism by which mesalamine causes symptomatic exacerbation of UC in certain affected patients.

CASE REPORT

A 28-year old woman with a history of UC presented to her primary care physician with complaints of fatigue, crampy abdominal pain, bloating and 2-3 episodes of bloody diarrhea per day. She was initially diagnosed with UC at the age of 20 years and treated with mesalamine for several months with complete resolution of symptoms. She self-discontinued the mesalamine after approximately six months secondary to occasional episodes of nausea which she attributed to the medication and has since re-

ported good health until this presentation. Her primary care physician completed an extensive workup and treated her symptoms with a two week taper of oral steroids and resumption of mesalamine (800 mg by mouth three times a day). An outpatient sigmoidoscopy was obtained which revealed shallow ulcers and continuous areas of inflammation beyond the view of the scope. Despite this treatment, her symptoms persisted and worsened. She began to have an increase in frankly bloody bowel movements up to 12-15 per day and reported a 10-pound weight loss. She is a lifelong non-smoker, has no other history of medical illnesses or surgeries, denies recent medication or non-steroidal anti-inflammatory use and has had no known sick contacts or infectious exposures. She has no extraintestinal manifestations of her disease. Her primary care physician recommended that she be admitted to the hospital for intravenous steroids, fluids and further management.

On admission, physical examination, laboratory data and abdominal radiographs were only significant for an elevated C-reactive protein and a hemoglobin level of 10.9 g/dL. Despite an initial improvement in her diarrhea, the patient continued to complain of persistent nausea and crampy abdominal pain, particularly after mesalamine administration. A surgical consultation was obtained and a repeat sigmoidoscopy confirmed previous endoscopic findings. Histological evaluation revealed acute inflammation with crypt architectural distortion diffusely consistent with inflammatory bowel disease, favoring UC. Stool studies were negative for infection. A computed tomography scan was obtained which suggested significant symmetrical bowel wall thickening with adjacent mesenteric inflammatory changes extending from the ascending colon to the rectum. After seven days of hospitalization, she continued to complain of nausea, abdominal pain and 4-6 bloody bowel movements per day. Over the course of the admission she became increasingly irritable and anxious. The correlation between the mesalamine administration and the nausea prompted a withdrawal of the mesalamine drug. Her bowel symptoms then improved significantly on the steroid monotherapy and after an additional three days of inpatient care, she was well enough to be discharged home on an oral steroid taper.

DISCUSSION

Sulfasalazine and other 5-aminosalicylic acid (5-ASA) compounds are used as mainstay drugs for the treatment of UC. Sulfasalazine was devised in the early 1940s by Dr. Nanna Svartz and consists of a 5-ASA molecule linked to a sulphapyridine moiety by an azo bond. Sulfasalazine is relatively safe and effective in inducing and maintaining remission from UC symptoms; however, up to 30% of patients cannot take it due to intolerance or hypersensitivity reactions which are often attributed to the sulphapyridine moiety[1]. Mesalamine, which is simply 5-ASA, lacks the sulphapyridine moiety and is better tolerated with fewer adverse reactions[2]. In 1977, Azad Khan *et al*[3] showed that mesalamine is as efficacious as sulfasalazine when used topically and several topical and delayed release oral compounds were subsequently developed. This case describes one of the few reported incidences of severe exacerbations of UC after administration of mesalamine, for which the pathogenesis is largely still unknown[3].

Most patients with intolerance to 5-ASA compounds experience systemic manifestations such as fever, nausea, vomiting, diarrhea and rashes, thought to be allergic drug reactions[4]. These reactions are rare, affecting only 8% of patients. Severe reactions include bone marrow suppression, arthritis, pneumonitis, pericarditis and pancreatitis[5]. Diarrhea is seen more commonly with olsalazine (13%), composed of two 5-ASA molecules linked by an azo bond, than with mesalamine (5%) and is attributed to a secretory mechanism secondary to the inhibition of ileal and colonic Na^+ K^+ ATPase which leads to malabsorption of sodium and water. This mechanism, however, does not explain the bloody diarrhea or the endoscopic and histological evidence of inflammation seen in this case[4,6].

Mesalamine, unlike sulfasalazine and non steroidal anti-inflammatory drugs (NSAIDs), is an uncommon cause of UC exacerbation. In order to confirm mesalamine as the causative agent, a mesalamine challenge can be performed. Two such challenges have been reported in patients who previously demonstrated mesalamine intolerance but were in remission at the time of the study. In 1995, Kapur *et al*[4] administered a mesalazine suppository to such a patient and subsequently induced bloody diarrhea within four hours. Prior to the challenge, biopsies taken from three sample sites showed typical chronic UC in remission with chronic inflammatory cells in the lamina propria but no evidence of a neutrophilic infiltrate or mucus depletion. After the challenge, biopsies demonstrated a diffuse neutrophilic infiltrate from the lamina propria to the crypt epithelium along with mucus depletion. Additionally, there was no evidence of any increased eosinophilia nor was there any evidence that pointed to a drug reaction rather than a relapse. Sturgeon *et al*[1] performed a similar rectal challenge in a patient with UC in remission. Biopsies taken before the challenge showed chronic UC and those taken after the challenge showed a neutrophilic and eosinophilic infiltrate of the lamina propria as well as crypt destruction. In both studies, there was endoscopic evidence of edema, erythema and punctate mucosal exudates, similar to that which was found in our patient[1,4]. In all of the reported cases of mesalamine exacerbated UC, there is no consistent pattern in the alteration of lab values. Some patients have lab values that remain unchanged whereas others, such as our patient, demonstrate increased inflammatory markers and/or leukocytosis. The means by which mesalamine causes these changes remains unknown as it lacks the sulphapyridine moiety implicated in sulfasalazine exacerbations[5].

Alteration of arachidonic acid metabolism is one proposed mechanism for mesalamine induced exacerbation of UC. In 1998, Fine *et al*[6] proposed that 5-ASA compounds might exacerbate colitis in patients with inflammatory bowel disease (IBD) by a mechanism similar to acetylsalicylic acid and NSAIDs due to their similar

structure[6]. In the rectal dialysates of patients with active IBD there are elevated levels of prostaglandins and leukotrienes[5]. NSAIDs alter arachidonic acid metabolism by inhibiting cyclooxygenase which causes a decrease in prostaglandin synthesis. However, there is a paradoxical increase in leukotriene synthesis as arachidonic acid is shunted into the lipoxygenase pathway, leading to intestinal inflammation and diarrhea. While *in vitro* studies demonstrate that mesalamine inhibits both the cyclooxygenase and the lipoxygenase pathways, Fine *et al*[6] analyzed the fecal eicosanoids of a patient with mesalamine exacerbated IBD and showed a 45% decrease in prostaglandin E_2 but a 500% increase in leukotriene B_4, similar to what would be expected with NSAID exacerbated colitis. Evaluation of fecal dialysates was not performed on the patient in this case. Furthermore, steroids, often used concomitantly in patients with UC exacerbations, inhibit phospholipase activity which causes a decrease in leukotrienes and can mask mesalamine intolerance until they are stopped[5].

Mesalamine intolerance does not indicate a global intolerance to all 5-ASA compounds. In a comparative study in which patients with UC intolerant to sulfasalazine were administered three 5-ASA compounds, mesalamine, olsalazine and balsalazide, 91% of patients were able to tolerate at least one of the three compounds. This study shows that even in patients intolerant to mesalamine, a trial of another 5-ASA compound may still be indicated[7].

Mesalamine is an efficacious and relatively safe drug that is widely used to treat UC. More research must be done to understand the mechanism by which mesalamine causes exacerbations of UC in certain patients. Physicians must remember to keep mesalamine on the differential for UC exacerbations, especially in patients who are recently started on the drug or those whose symptoms appear after withdrawal of steroids.

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CASE REPORT

Intestinal pseudo-obstruction in inactive systemic lupus erythematosus: An unusual finding

Giulia Leonardi, Nicola de Bortoli, Massimo Bellini, Maria Gloria Mumolo, Francesco Costa, Angelo Ricchiuti, Stefano Bombardieri, Santino Marchi

Giulia Leonardi, Nicola de Bortoli, Massimo Bellini, Maria Gloria Mumolo, Francesco Costa, Angelo Ricchiuti, Santino Marchi, Gastroenterology Unit, Cisanello Hospital, University of Pisa, Via Paradisa 2, 56124 Pisa, Italy
Stefano Bombardieri, Reumatology Unit, Hospital of Santa Chiara, University of Pisa, Via Roma, 56126 Pisa, Italy
Author contributions: Mumolo MG and Costa F designed the research; Ricchiuti A performed the research; Bombardieri S and Marchi S analyzed the data; Leonardi G, Bellini M and de Bortoli N wrote the paper.
Correspondence to: Giulia Leonardi, MD, Gastroenterology Unit, Cisanello Hospital, University of Pisa, Via Paradisa 2, 56124 Pisa, Italy. giulialeonardi@alice.it
Telephone: +39-50-997435 Fax: +39-50-997436
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Abstract

Chronic intestinal pseudo-obstruction (CIP) is an infrequent complication of an active systemic lupus erythematosus (SLE). We illustrate a case of SLE inactive-related CIP. A 51-year old female with inactive SLE (ECLAM score 2) was hospitalized with postprandial fullness, vomiting, abdominal bloating and abdominal pain. She had had no bowel movements for five days. Plain abdominal X-ray revealed multiple fluid levels and dilated small and large bowel loops with air-fluid levels. Intestinal contrast radiology detected dilated loops. CIP was diagnosed. The patient was treated with prokinetics, octreotide, claritromycin, rifaximin, azathioprine and tegaserod without any clinical improvement. Then methylprednisolone (500 mg iv daily) was started. After the first administration, the patient showed peristaltic movements. A bowel movement was reported after the second administration. A plain abdominal X-ray revealed no air-fluid levels. Steroid therapy was slowly reduced with complete resolution of the symptoms. The patient is still in a good clinical condition. SLE-related CIP is generally reported as a complication of an active disease. In our case, CIP was the only clinical demonstration of the SLE.

Key words: Chronic intestinal pseudo-obstruction; Systemic lupus erythematosus

Peer reviewer: Dolores B Njoku, MD, Associate Professor, Division of Pediatric Anesthesiology and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins School of Medicine, 600 North Wolfe Street, Blalock 906A, Baltimore, MA 21287, United States

Leonardi G, de Bortoli N, Bellini M, Mumolo MG, Costa F, Ricchiuti A, Bombardieri S, Marchi S. Intestinal pseudo-obstruction in inactive systemic lupus erythematosus: An unusual finding. *World J Gastrointest Pharmacol Ther* 2010; 1(6): 135-136 Available from: URL: http://www.wjgnet.com/2150-5349/full/v1/i6/135.htm DOI: http://dx.doi.org/10.4292/wjgpt.v1.i6.135

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with a wide spectrum of multisystemic presentations[1]. Chronic intestinal pseudo-obstruction (CIP) is a complication that usually occurs during active SLE and is characterised by ineffective intestinal propulsion without any mechanical obstruction of the gut[2]. It is caused by the involvement of visceral smooth muscle and enteric nervous system and can be further classified as idiopathic or secondary. A secondary CIP can be induced by neurological, muscular, endocrine, metabolic and connective tissue diseases, infective agents and drugs[3].

CASE REPORT

A 51-year old female with a 13-year history of SLE (ACR criteria 1997) and nephrotic syndrome was hospitalized

after the onset of postprandial fullness with vomiting, abdominal bloating, dysphagia with solid foods and abdominal pain with cramps. She had had no bowel movements for five days.

Physical examination disclosed abdominal tenderness and distended abdomen with absent bowel sounds. She had been unsuccessfully treated with common prokinetics at the maximum dosage. Nasogastric probe and rectal tube were positioned. Cyclosporine (5 mg/kg per day), esomeprazole (40 mg daily), rifaximin (600 mg daily) and gentle enemas were started.

Blood tests showed slight anemia and leukopenia with reduction of serum proteins. Plasmatic levels of RCP, ERV, IgG and IgA were increased. The other laboratory tests were normal including urea nitrogen, creatinine, C3, C4 and CH50.

An upper digestive endoscopy was performed which detected esophagitis grade A according to the Los Angeles Classification and antral gastritis (H.P. negative).

Plain abdominal X-ray revealed multiple fluid levels and dilated small and large bowel loops with air-fluid levels. Ultrasound scan and abdominal computed tomography scan showed gastric distension and circumferential thickening of the large bowel without mechanical obstruction. Intestinal contrast radiology with soluble material detected dilated loops with very slow transit. Esophageal and ano-rectal manometry were performed to rule out scleroderma and Hirschsprung's disease respectively.

On the basis of these findings, chronic intestinal pseudo-obstruction was suspected and the patient was treated with octreotide (50 mg daily), clarithromycin (500 mg daily), rifaximin (1200 mg daily) and azathioprine (100 mg daily) without any clinical improvement. Tegaserod (6 mg bid) was also added without any positive effect.

Then an intravenous bolus of methylprednisolone (500 mg daily) was planned for three days. Quickly after the first administration the patient reported peristaltic movements. A bowel movement was reported after the second administration and a plain abdominal X-ray revealed no air-fluid levels. After the third bolus of 500 mg, it was decided to decrease the methylprednisolone to 100 mg iv daily for a week. After a few days, the abdominal tenderness and distension completely disappeared and abdominal sounds were clearly present. Over the next weeks, the steroid therapy was slowly but constantly reduced with a good response and a complete resolution of the symptoms. The patient is still in a good clinical condition.

DISCUSSION

SLE can involve each part of the gastrointestinal tract with oral aphthosis, esophageal dysmotility, mesenteric vasculitis, protein-losing enteropathy and pancreatitis as the most frequent manifestations[4]. Gastrointestinal involvement in SLE is rare. Apart from the mucosal involvement, the frequency of GI manifestations is very low.

CIP has been recognized as an uncommon and poorly understood complication of SLE: it usually occurs during active lupus (it can appear as a complication or as the initial presentation of SLE) but may manifest itself in inactive lupus. Until now, only 27 cases of SLE related CIP have been reported in literature[2].

This is the only SLE-related case of CIP in our experience. We started to treat the patient for a motility intestinal disorder because, on the basis of the clinical and serological criteria, the disease was inactive (ECLAM score 2)[5]. After the failure of a targeted motility approach, we considered the autoimmune disease as the core of the problem and the patient was successfully given a steroid therapy. SLE-related CIP, generally unusual, is reported as a complication of an active disease and favourably responds to high doses of corticosteroids[6]. In our case, CIP was the only clinical demonstration of the SLE.

Also, in inactive SLE, it is mandatory to start steroid therapy when CIP fails to respond to a targeted motility therapy.

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Giuseppe Brisinda, MD, Catholic Medical School, University Hospital "Agostino Gemelli", Largo Agostino Gemelli 8, Rome 00168, Italy

Yu-Jui Yvonne Wan, PhD, Professor, Liver Center, Room 4059 KLSIC, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160-7417, United States

Katsuyuki Nakajima, PhD, President and CEO, Nakajima and Associates, Co., Ltd., 3-33-2, Minami-cho, Maebashi Gunma 371-0805, Japan

P Hemachandra Reddy, PhD, Neurogenetics Laboratory, Neuroscience Division, Oregon National Primate Research Center, West Campus, Oregon Health and Science University, 505 NW 185th Avenue, Beaverton, OR 97006, United States

Bo Shen, MD, FACG, Digestive Disease Institute-Desk A31, The Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, United States

Norihiro Furusyo, MD, PhD, Department of General Internal Medicine, Kyushu University Hospital, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

Takashi Kawai, MD, PhD, Professor, Endoscopy Center, Tokyo Medical University 6-7-1, Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan

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Meetings

Events Calendar 2010

January 15-16, 2010
AGA Clinical Congress of Gastroenterology and Hepatology
Las Vegas, United States
http://www.gilearn.org/clinicalcongress

February 4, 2010
New Developments in Pain Therapy sponsored by the Swiss Society of Pharmacology and Toxicology
Bern, Switzerland
http://pharmacology.unibe.ch/SSPT2010

February 5-9, 2010
Cancer Genomics, Epigenomics & the Development of Novel Therapeutics
Waikoloa, United States

February 7-10, 2010
53rd Annual Meeting of the Western Pharmacology Society
San Diego, United States
http://www.medicine.nevada.edu/wps/annualmeeting.html

February 25, 2010
Multidisciplinary management of acute pancreatitis symptoms
London, United Kingdom
http://www.rsm.ac.uk/academ/pancreatitis10.php

March 16-18, 2010
83rd Annual Meeting of the Japanese Pharmacological Society
Osaka, Japan
http://www2.convention.co.jp/83jps/english/english_top.html

March 17-20, 2010
Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics
Atlanta, United States
http://www.ascpt.org/annualmeeting2010/index.cfm

March 23-25, 2010
51st Annual Meeting of the German Society for Experimental and Clinical Pharmacology and Toxicology
Mainz, Germany
http://www.pharmakologie.uni-mainz.de/JTG/JTG.html

March 25-28, 2010
20th Conference of the Asian Pacific Association for the Study of the Liver
Beijing, China
http://www.apasl2010beijing.org/en/index.aspx

May 15, 2010
Digestive Disease Week 2010
New Orleans, United States
http://www.ddw.org/

June 2-4, 2010
Annual meeting of the Canadian Society of Pharmacology and Therapeutics
Toronto, Canada
http://www.pharmacologycanada.org

July 16-17, 2010
WorldPharma2010 Satellite Meeting: The role of clinical pharmacology in therapeutic drug monitoring and clinical pharmacogenetics
Copenhagen, Denmark

July 17-23, 2010
16th World Congress on Basic and Clinical Pharmacology (WorldPharma2010)
Copenhagen, Denmark
http://www.WorldPharma2010.org

September 12-14, 2010
39th Annual Meeting of the American College of Clinical Pharmacology
Baltimore, United States
http://www.accp1.org

September 23-26, 2010
The 1st World Congress on Controversies in Gastroenterology & Liver Diseases
Prague, Czech

October 15-20, 2010
ACG 2010: American College of Gastroenterology Annual Scienitfic Meeting
San Antonio, United States

October 20-23, 2010
Australian Gastroenterology Week
Melbourne, Australia
http://www.gesa.org.au/agw.cfm

November 11-12, 2010
20th Neuropharmacology Conference co-organized by the Nomenclature Committee of IUPHAR (NC-IUPHAR): Receptor Structure and Drug Design
San Diego, United States
http://www.neuropharmacology-conference.elsevier.com

November 13-14
Case-Based Approach to the Management of Inflammatory Bowel Disease
San Francisco, United States

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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