

Protective effect of *Matricaria Chamomilla* extract on hepatic-renal toxicity of ceftriaxone in rats

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Abstract

The effect of *Matricaria chamomilla* (M.chamomilla) against hepatic-renal toxicity of Ceftriaxone was investigated in this study. Twenty eight rats were divided into four groups. The 1st group was injected with saline as control, the 2nd and 3rd groups were injected with M.chamomilla extraction (50mg/kg.b.wt) andwith ceftriaxone (180 mg/kg.b.wt.) for two and one week respectively while the 4th group was injected with M.chamomilla extraction plus ceftriaxone. at dose 50mg/kg and 180 mg/kg.b.wt respectively ,daily for the one week and with M.chamomilla extraction only at dose 50mg/kg.b.wt for another week. At the end of the 1st week, the 3rdgroup had significantly higher ALP,ALT,AST, urea and creatinine levels with significantly lower albumin and A/G ratio levels than that of the 1stand2ndgroups , while the 4th group did not differ from 1stand 2ndgroups in terms of these parameters. Histopathological studies revealed that, the 3rd group had some pathological changes in the liver and kidney. From this study we can conclude that, M. chamomilla extraction can reduce hepatic-renal toxicity of ceftriaxone in rats.

Keywords: Ceftriaxone; *Matricaria Chamomilla*; Biochemical Changes; Histopathological.

1. Introduction

Chamomile is one of the most common herbs which used for medicinal purposes (Janmejai et al. 2010). There are numerous types of Chamomile, Roman Chamomile and German Chamomile is the most two popular. German Chamomile called *Matricaria chamomilla* which considered the more potent and received more scientific evaluation (Ragaa et al. 2011). Some chamomile biological effects were confirmed in experimental models and clinical studies (Vandross et al. 2003, Fabian et al. 2011). The dried flowers of chamomile contain many terpenoids and flavonoids that contribute to its medicinal properties (Janmejai et al. 2010). There are different preparations of chamomile that have developed; the most popular one is in the form of herbal tea. Biological effects of chamomile have been confirmed in different experimental models and clinical studies (Vandross et al. 2003)

Ceftriaxone is a bactericidal cephalosporin which is a third – generation, resistant to various types of bacterial β -lactamases; it has effect against Gram-negative and Gram-positive bacteria including Enterobacteriaceae, Haemophilus influenza, Streptococcus pneumoniae (Matsuzaki et al. 2005). Ceftriaxone inhibit enzymes that are called transpeptidase enzymes which are responsible for the final step in bacterial cell wall synthesis which has significant stability against beta-hydrolysis (Neu. 1985).

Ceftriaxone is wide distribution in tissues and has rapid absorption as well as body fluids; it is extremely useful in a variety of infectious diseases including meningitis, septicemia, urinary tract, respiratory tract and joints infections (Gohil et al. 2009). Ceftriaxone is widely used in human medicine because of it has prolonged terminal half-life (5.4-8.2h) which allows its prescription on a single administration per day (Bourget et al. 1993). Ceftriaxone

undergoes hydrolysis to form active metabolite ceftizoxime in goat (Sar et al. 2006). Ceftizoxime undergoes biotransformation in liver to inactive form metabolite resulting in decrease concentration in blood (Sar et al. 2006, Bakul et al. 2009). The drug is primarily eliminated via the kidneys (33-67%) with remainder eliminated via the biliary system and bind with calcium ions producing biliary pseudolithiasis(Avci et al. 2016). The liver eliminates a considerable proportion of ceftriaxone in the form of a soluble salt (Avci et al. 2016), ceftriaxone is an anion when its concentration become high these anions bind with calcium ions to form insoluble complexes that precipitate out the biliary system (Shiffman et al. 1990, Park et al. 1991)

Combination of herbs with chemotherapy may be used to decrease adverse effects, elevate the immune function and improve the quality of life in the patients (Ragaa et al. 2011).

Hypothesis of this study is *Matricaria Chamomilla* extract has protective effect on hepato-renal toxicity which induced during ceftriaxone injection in male albino rats by monitoring the biochemical changes in serum and histopathological findings in liver and kidney.

2. Material and methods

2.1. Drug

2.1.1. Ceftriaxone

Ceftriaxone is a white to yellowish –orange crystal line powder which is soluble in water, produced by Pharco B International for Novartis Pharma.S.A.E. Cairo, Egypt. The drug is supplied for

intramuscular or intravenous administration in strengths equivalent to 250 mg, 500 mg and 1 gram of ceftriaxone sodium.

2.1.2. Preparation of crude extract of *Matricaria chamomilla*

M. chamomilla is selected with a fair degree of quality assurance from the farm of Sekem Company (Belbeis Desert Road) which identified by Medicinal and Aromatic Plants Research Department, National Research Centre. Flowering heads were subjected for shade drying then they were powdered. Fifty grams of powdered flowering heads were extracted with 500 ml of 70% ethyl alcohol for two days. The mixture was sonicated for one hour then the mixture was filtrated. The previous steps were repeated twice on the flowering heads residues. The whole filtrates were concentrated with rotary evaporator on 50°C under vacuum until the solution (alcohol + water) was completely removed (Sukhdev et al. 2008). Concentrated extract was weighed and dissolved in known quantity of saline to prepare a stock solution of 50 mg ml⁻¹ concentration and then stored at 4°C.

2.2. Experimental design

Twenty eight adult male albino rats (150-200 gram) obtained from the Animal House, Faculty of Veterinary Medicine, Benha University, Egypt. Rats were housed in clean cages and fed with standard pellet diet and tap water ad libitum, each rat was kept in single metabolic cages under a 12 hr light/dark cycle. Rats acclimatized to the environment for one week before to experimental use.

Rats were divided in four groups, each of seven rats. The 1st group considered as control group was injected with saline intramuscular (IM) once daily for two weeks, the 2nd group was injected with *M. chamomilla* extraction intra peritoneal (IP) at dose (50mg/kg) once daily for two weeks, the 3rd group was injected intramuscularly with ceftriaxone at dose 180 mg/kg.b.wt. once daily for one week and the 4th group was injected with ceftriaxone at dose 180 mg/kg.b.wt. intramuscularly for one week only plus *M. chamomilla* extraction intra peritoneal (IP) at dose (50mg/kg) daily for two weeks. Blood samples were obtained from the retro-orbital venous plexus. The samples were collected into plain centrifuge tube to separate serum for biochemical analysis. Duration of sample collection from each group was after one and two weeks from the beginning of experiment for biochemical parameters.

2.3. Biochemical evaluation

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) were measured according to the method of (Reitman et al., 1957), serum alkaline phosphatase (ALP) was measured according to the method of (Glick et al., 1986), Total protein according to (Weichselbaum, 1946), albumin was measured according to the method of (Maier et al., 2007), urea and creatinine were determined in serum using kits from Diamond Diagnostic. Egypt Company, all measured by spectrophotometer

2.4. Histopathology

At the end of the 2nd week, all animals sacrificed for tissue sampling. Liver and kidney specimens were fixed in 10% buffered neutral formalin for histopathological examination. Importantly, tissue samples were also collected after one week from ceftriaxone group

2.5. Statistical analysis

Data was statistically analyzed by ANOVA with post hoc Duncan multiple comparison test using statistical software program (SPSS for Windows version 20, USA). Differences were considered significant at $p < 0.05$.

3. Results

3.1. Biochemical results

Concerning to the changes in liver enzymes, ALT, AST and ALP after one week, this study confirmed that there was significant increase ($p < 0.05$) in ALT, AST and ALP levels in ceftriaxone group when compared with control group. Meanwhile there were no significant changes in *Matricaria chamomilla* group in comparison with control group. Ceftriaxone plus *Matricaria chamomilla* group showed significant decrease ($p < 0.05$) in ALT, AST and ALP levels when compared with ceftriaxone group as shown in Table 1.

After two weeks, there were no significant changes in ALT, AST and ALP levels in *M. chamomilla* group, ceftriaxone group and ceftriaxone plus *M. chamomilla* group when compared with control group. Similarly, the levels of ALT, AST and ALP enzymes in ceftriaxone plus *M. chamomilla* group showed no significant changes in comparison with ceftriaxone group.

Regarding to the changes in total protein, albumin and globulins levels, there were no significant changes in different groups after one week. On the other hand, after two weeks, there were no significant changes in total protein, albumin and globulins levels in *M. chamomilla* group and ceftriaxone plus *M. chamomilla* group when compared with control group. Meanwhile, ceftriaxone group showed significant decrease in albumin level associated with no significant changes in total protein and globulin levels in comparison with control group. Importantly, the levels of albumin and A/G ratio were significantly increased in ceftriaxone plus *M. chamomilla* group when compared with ceftriaxone group.

The levels of urea and creatinine after one week showed no significant changes in *M. chamomilla* group and Ceftriaxone plus *M. chamomilla* group when compared with control group. Meanwhile, urea and creatinine levels were significantly increased in ceftriaxone group in comparison with control group. On the other hand, ceftriaxone plus *M. chamomilla* group showed significant decrease in urea level associated with no significant changes in creatinine level when compared with ceftriaxone group.

Determination of urea and creatinine levels revealed no significant changes between different groups after two weeks.

3.2. Histopatholog results

Liver consisted of hepatic cords around central vein (Fig.1) in control group. Liver showed hydropic degeneration, periductal fibrosis and periductal cell infiltration was noticed around the portal ducts (Fig.2) with mild portal fibrosis and congestion in the portal blood vessels (Fig.3) in Ceftriaxone group after one week, while in Ceftriaxone group after two week, the hepatic tissue showed proliferation in the von kupfer cells (Fig.4). In *M. chamomilla* group, liver consisted of hepatic cords around central vein. No pathological changes in the architecture of the hepatic tissue (Fig.5) while in Ceftriaxone plus *M. chamomilla* group, the hepatic tissues showed patches of hydropic degeneration and congestion in the portal veins (Fig.6).

Kidney consisted of renal corpuscles (Bowman's capsule) and renal tubules (PCT, DCT, Collecting ducts and connecting pieces (Fig.7) in Control group. The renal tubules were occupied by eosinophilic hyaline casts that obscured the underlying structure (Fig.8) with congestion and edema was noticed in the renal blood vessels (Fig.9) and cloudy swelling in the renal tubules in Ceftriaxone group after one week while, in Ceftriaxone group after two week there is hyaline degeneration was located in the cuboidal cells of the renal tubules (Fig.10). The kidney had the same histological structure as that of the control group with no pathological changes were noticed in the architecture of the renal tissues (Fig.11) in *M. chamomilla* group, while, Ceftriaxone plus *M. chamomilla* group the renal blood vessels showed congestion and cloudy swelling in the renal tubule (Fig.12).

Table 1: Serum Biochemical Parameters (Mean±SE) in Control, Matricaria Chamomilla, Ceftriaxone and Combined Group after One Week

	Control	M. chamomilla	Ceftriaxone	Ceftriaxone+ M.chamomilla
ALT (U/I)	65.34±4.81 ^b	68.91±2.75 ^b	93.57±5.99 ^a	71.93±4.12 ^b
AST (U/I)	150.28±4.34 ^b	178.42±10.47 ^b	226.14±12.91 ^a	172.14±9.31 ^b
ALP (U/I)	205.0±2.88 ^c	219.42±8.37 ^c	355.57±13.97 ^a	257.28±12.13 ^b
Total Protein(g/dl)	7.16±0.21 ^{a,b}	6.59±0.37 ^b	7.12±0.39 ^{a,b}	7.68±0.25 ^a
Albumin (U/I)	3.61±0.20 ^a	3.21±0.17 ^a	3.59±0.22 ^a	3.34±0.18 ^a
Globulin (U/I)	3.55±0.35 ^a	3.38±0.40 ^a	3.52±0.39 ^a	4.34±0.39 ^a
A/G Ratio	1.11±0.18 ^a	1.02±0.11 ^a	1.10±0.14 ^a	0.83±0.11 ^a
Urea (mg/l)	16.68±0.37 ^b	16.82±1.03 ^b	20.80±0.71 ^a	17.24±1.46 ^b
Creatinine (mg/l)	0.72±0.056 ^b	0.75±0.04 ^b	1.00±0.057 ^a	0.84±0.05 ^{a,b}

Means in the same row with different superscript letters are significantly different at P < 0.05.

Table 2: Serum Biochemical Parameters (Mean±SE) in Control, Matricaria Chamomilla, Ceftriaxone and Combined Group after Two Weeks

	Control	M. chamomilla	Ceftriaxone	Ceftriaxone+ M.chamomilla
ALT (U/I)	75.71±3.80 ^a	70.71±8.04 ^a	76.14±3.64 ^a	72.00±2.63 ^a
AST (U/I)	205.28±33.13 ^a	235.60±14.47 ^a	238.0±18.27 ^a	227.50±13.01 ^a
ALP (U/I)	243.28±11.98 ^a	265.42±6.12 ^a	274.28±21.36 ^a	276.42±13.31 ^a
Total Protein (g/dl)	6.44±0.18 ^a	6.20±0.14 ^a	6.01±0.16 ^a	6.15±0.30 ^a
Albumin (U/I)	3.24±0.18 ^a	3.24±0.18 ^a	2.37±0.23 ^b	3.29±0.14 ^a
Globulin (U/I)	3.19±0.17 ^a	2.96±0.14 ^a	3.64±0.26 ^a	2.86±0.35 ^a
A/G Ratio	1.03±0.09 ^{a,b}	1.12±0.10 ^{a,b}	0.70±0.13 ^b	1.33±0.26 ^a
Urea (mg/l)	24.69±2.43 ^a	27.72±2.42 ^a	32.71±2.79 ^a	26.07±1.91 ^a
Creatinine (mg/l)	0.92±0.01 ^a	0.85±0.03 ^a	0.91±0.01 ^a	0.83±0.04 ^a

Means in the same row with different superscript letters are significantly different at P < 0.05.

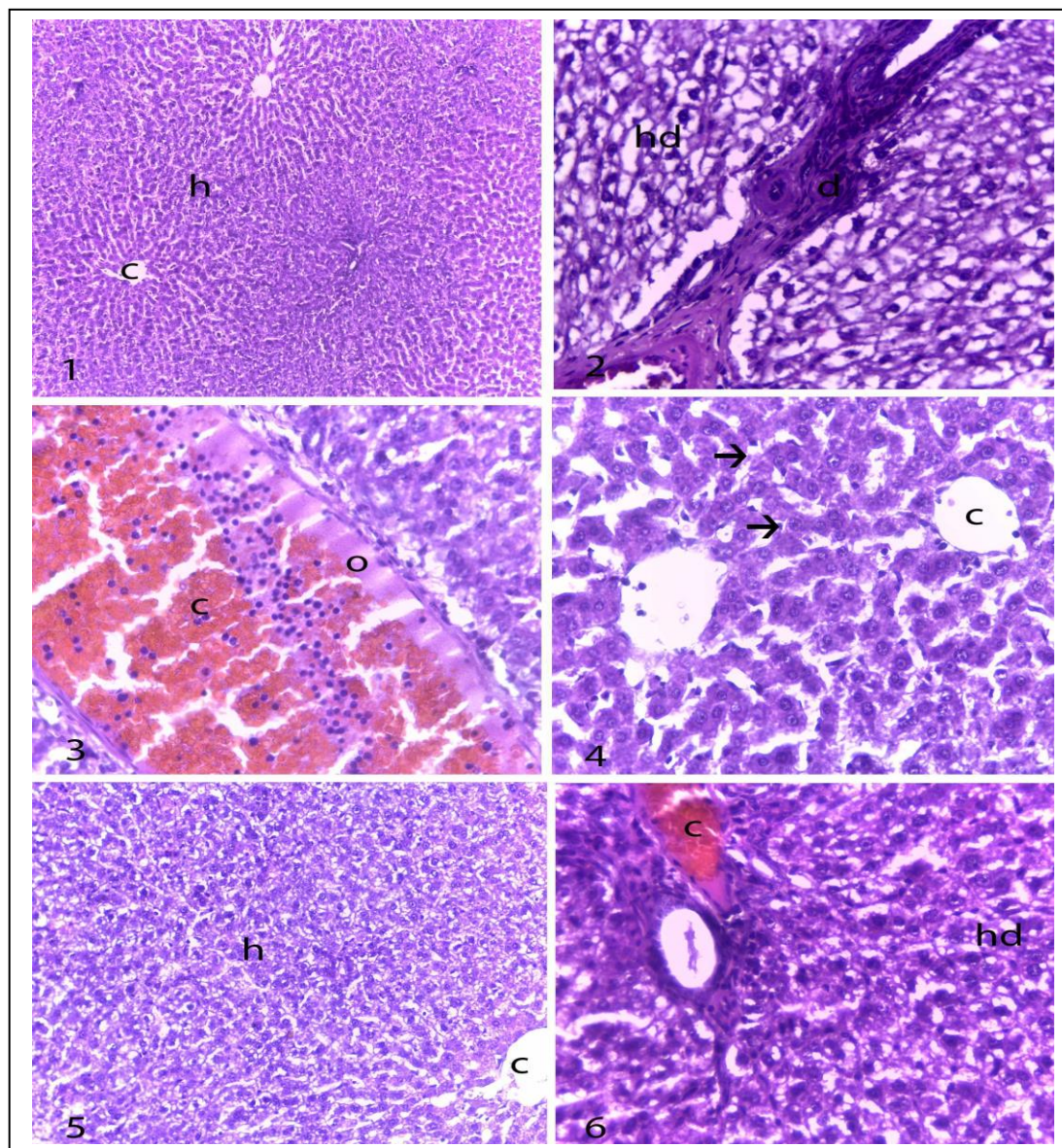


Fig. 1: Liver of the Control Group Showed Central Vein (C) and Hepatic Cord (H) H&E X10. Fig.2. Liver of Ceftriaxone Group Treated by 180mg/Kg.B.Wt/M (1 Week) Showed Hydropic Degeneration (Hd) and Periductal Fibrosis (D) H&E X20. Fig.3. Liver of Ceftriaxone Group (1 Week)

Showed Congestion (C) and Edema (O) C H&E X40. Fig.4. Liver of Ceftriaxone Group (2 Weeks) Showed Proliferation of Von Kupfer Cells (Arrows).H&EX20. Fig.5. Liver of Chamomile Group Treated by 50mg/Kg.B.Wt/P Showed Normal Histological Structure, Central Vein (C) And Hepatic Cord (H) H&E X10. Fig.6. Liver of Ceftriaxone and Chamomile Group Showed Congestion of Blood Vessels (C) and Patches of Hydropic Degeneration (Hd) H&E X20.

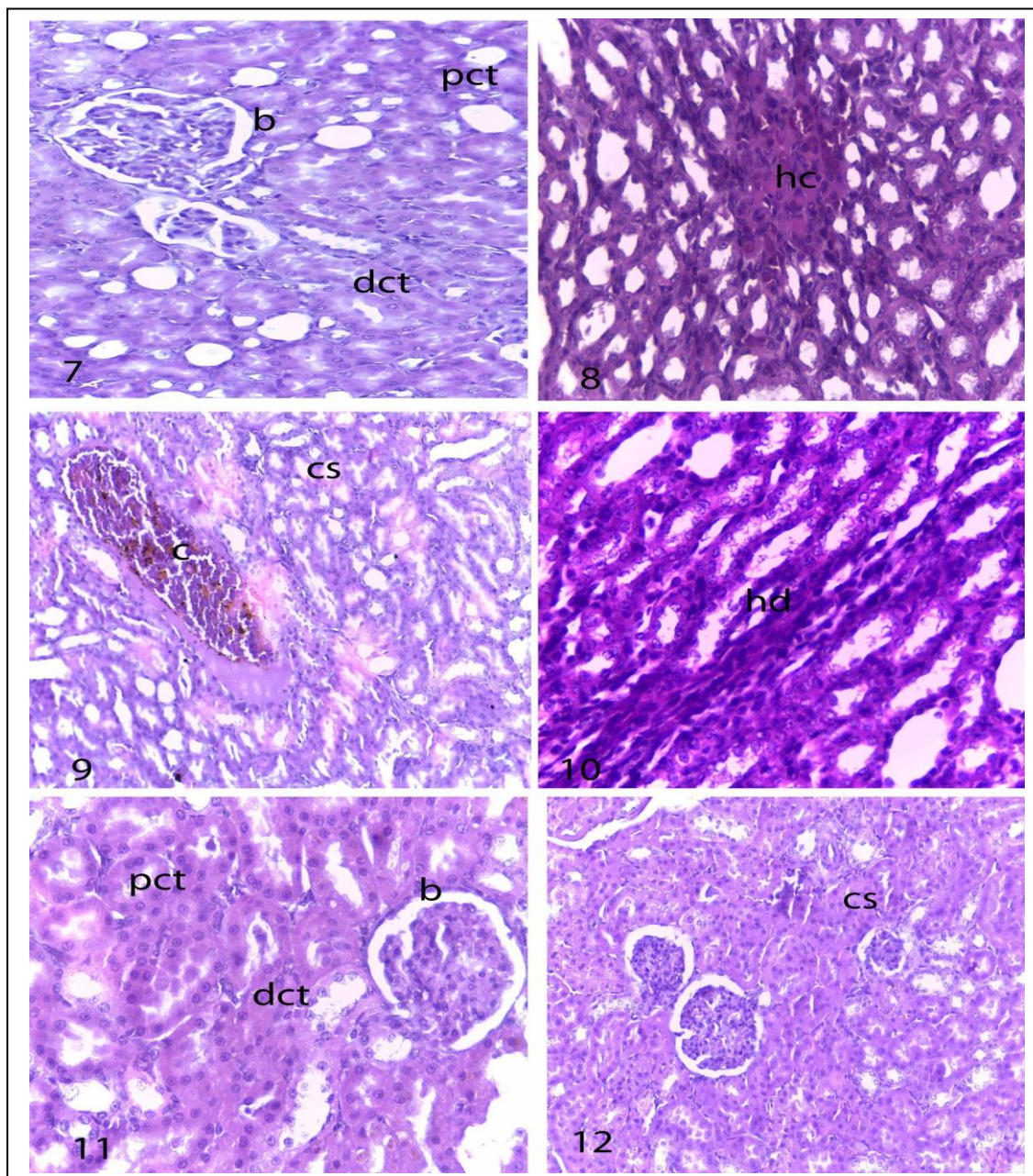


Fig. 7: Kidney of the Control Group Bowman's Capsule (B), Proximal Convoluted Tubules (Pct) and Distal Convoluted Tubules (Dct) H&E X10. **Fig. 8:** Kidney Of Ceftriaxone Group Treated By 180mg/Kg.B.Wt/M (1 Week) Showed Eosinophilic Hyaline Casts (Hc) H&E X20. **Fig. 9:** Kidney of Ceftriaxone Group (1 Week) Showed Congestion (C) and Edema and Cloudy Swelling (Cs) H&E X20. **Fig. 10:** Kidney of Ceftriaxone Group (2 Weeks) Showed Hyaline Degeneration in the Renal Tubules Cells (Hd) H&E X20. **Fig. 11:** Kidney of Chamomile Group Treated by 50 Mg/Kg.B.Wt/P Showed Bowman's capsule (B), Proximal Convoluted Tubules (Pct) and Distal Convoluted Tubules (Dct) H&E X10. **Fig. 12:** Kidney of Ceftriaxone and Chamomile Group Showed Cloudy Swelling of the Renal Tubules (Cs) H&E X20.

4. Discussion

Ceftriaxone used as a third generation cephalosporin antibiotic which has a broad spectrum of bactericidal activity (Rajpurohit et al. 2012). The most sensitive biochemical markers in the diagnosis of hepatic dysfunction are AST, ALT, ALP (Nnodim et al. 2010). In this study, there were significant elevation of serum AST and ALT levels in group treated with ceftriaxone for one week. These data indicate severe damage in the liver which is supported by histopathological examination that showed hydropic degeneration and periductal fibrosis. These results consistent with (Malomo,

2000; Ramkumar et al. 2003, Bakul et al. 2009, Elsayed et al. 2011a, Khaled et al. 2014). Also, there is a number of evidence found that ceftriaxone has adverse effects as elevation of the liver enzyme, liver injury, cholestatic abnormalities (Reddy et al. 1995, Elsayed et al. 2011a, Bhamidimarri et al. 2013). Elevation of AST and ALT may be attributed to increased permeability of hepatocyte due to pathological changes in liver tissues which lead to escape of liver tissue enzymes into circulating blood (Bakul et al. 2009). Histopathological findings in this study were consistent with (Khaled et al. 2014) who recorded that injection of ceftriax-

one at 180 mg/kg induced diffuse hydropic degeneration in the hepatocytes of per portal area in rat.

On the hand, the degree of liver damage in group received *M. chamomilla* during administration of Ceftriaxone showed mild degree of hepatic damage which evidenced by histopathological findings that revealed hydropic degeneration of hepatocytes. Protective effect of *M. chamomilla* may be attributed to its antimicrobial and moderate antioxidant activities in vitro (Ragaa, 2012). Furthermore, in vivo studies showed that *M. chamomilla* has potent anti-inflammatory action, cholesterol lowering activities and some antimutagenic as well as antispasmodic effects (McKay et al. 2006). Also may be due to bisabololoxide A which is the principle ingredient of German chamomile that has anti-inflammatory action (Ogata et al. 2010, Ragaa et al. 2011, Ragaa, 2012). These findings are in accordance with (Saleem et al. 2010) who reported that the ethanolic extraction of chamomile recutita has reversal effects on liver glutathione, serum bilirubin and serum marker enzymes in hepatotoxicity induced by paracetamol and attributed these results to the hepatoprotective effect of chamomile.

There was significant elevation of serum ALP in this study in group treated by ceftriaxone for one week. This result was similar to that obtained with (Elsayed et al. 2011a) and this elevation related to hepatic cell damage which confirmed by histopathology results (Moss et al. 1974, Gaw et al. 1999). Meanwhile, (Saganuwan. et al. 2006) recorded that AST, ALT and ALP were not affected significantly after intravenous injection of ceftriaxone in turkey. Coadministration of *M. chamomilla* with ceftriaxone to rats markedly induces reduced serum ALP which manifested histopathologically by improvement in liver tissues lesions. These results may be attributed to the flowers of chamomile contain 1-2% volatile oils including alpha-bisabololoxids A and B, alpha-bisabolol and matricin which converted to chamazulene and other flavonoids which has anti-inflammatory and antiphlogistic properties (Carnat et al. 2004, Janmejai et al. 2010).

There were no significant changes in total protein, albumin and globulins levels in different groups after one week compared with control group. Meanwhile, ceftriaxone group showed significant decrease in albumin level associated with no significant changes in total protein and globulin levels in comparison with control group after two weeks only. These results consistent with (Elsayed et al. 2011a) who reported that serum albumin level decrease after injection of ceftriaxone in rat. These results may be attributed to ceftriaxone displaced bilirubin from albumin so that it used with caution in jaundiced newborns (Gillian et al. 1987), while (Saganuwan. et al., 2006) recorded that albumin and total protein showed no significant changes after intravenous injection of ceftriaxone in turkey. While the levels of albumin and A/G ratio were significantly increased in ceftriaxone plus *M. chamomilla* group after one week when compared with ceftriaxone group which confirmed with our histopathology results in which improvement in liver tissue lesions which attributed to one of chamomile's anti-inflammatory activities include the inhibition of LPS-induced prostaglandin E(2) release and attenuation of cyclooxygenase (COX-2) enzyme activity without affecting the constitutive form, COX-1 (Srivastava et al. 2009, Janmejai et al. 2010).

Concerning kidney function, there were no significant changes in urea and creatinine levels in *M. chamomilla* group compared with control group after one week and two weeks. Ceftriaxone group showed significant increase in urea and creatinine levels in comparison with control group after one week of treatment. These results supported by histopathological examination that revealed congestion and edema in the renal blood vessels and cloudy swelling in the renal tubules. These results were consistent with (Elsayed et al. 1997, Kohda et al. 2005, Elsayed et al. 2011b). Meanwhile, ceftriaxone plus *M. chamomilla* group showed no significant changes in urea and creatinine levels when compared with control group after one week. This results consistent with (Ragaa, 2012) recorded that administration of *M. chamomile* extract with cisplatin provided protection for the kidney by decreasing urea and creatinine levels in serum of rat. These finding indicate that *M. chamomile* extract has protective effect on renal

tissues especially when administrated during Ceftriaxone treatment. *M. chamomile* extract protected the kidney tissues from effect of ceftriaxone which may be attributed to chamomile's anti-inflammatory activities (Srivastava et al. 2009, Janmejai et al. 2010). Chamazulene and flavonoid-apigenin constituents of chamomile extract were been shown to exert anti-inflammatory activity in vivo and in vitro (Shipochliev et al. 1981, Verbeek et al. 2004, McKay et al. 2006). In addition to chamomile and its components have antioxidant effects (McKay et al. 2006).

It is worth mentioned that, the biochemical changes and histopathological finding obtained after two weeks in ceftriaxone group showed improvement in comparison with that obtained after one week in the same group. These results came in agreement with (Bakul et al. 2009) who reported that the residual concentration of ceftriaxone and its metabolite ceftizoxime in blood and various tissues showed a decreased pattern after 7 days onwards..

5. Conclusion

Co administration of *Matricaria chamomile* extraction with ceftriaxone to rats has protective effect against hepatic-renal injury which induced during treatment with ceftriaxone especially with whom suffering from liver and kidney dysfunctions.

6. Acknowledgments

The authors grateful to HEND FOUD ESMail, Assistant researcher, Medicinal and Aromatic Plants Research Department, National Research Centre for her advice and help during extraction in this study.

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