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NEPHROPROTECTIVE ACTIVITY OF MATRICARIA CHAMOMILE AND CURCUMA LONGA AQUEOUS EXTRACTS ON TETRACYCLINEE-INDUCED NEPHRO-TOXICITY IN ALBINO RATS

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ABSTRACT

This study was carried out to investigate the influences of oral administration of aqueous extract of *Matricaria chamomile* and *curcumin* in nephrotoxicity induced in rats by Tetracyclinees for 4 weeks. The effects were determined via estimation of kidney functions and hitopathological changes. Rats were divided into six groups (6 rats each). The first group (G1) were healthy animals treated by Distal Water (DW, IP). In groups 2-6, nephrotoxicity was induced by Tetracycline (25 mg/ kg BW IP), Group 2 treated by DW, groups 3 and 5 rats treated with either *Matricaria chamomile* extract or *curcumin* (50 mg/kg BW and 200mg/kg BW respectively) without disease induction, while the animals in groups 4 and 6 were received a combination of full dose of *Matricaria chamomile* or *curcumin* with Tetracyclinee for 14 days. Tetracycline nephrotoxicity associated with significant increase in the serum urea, createnine Na^+ and K^+ with significant (P<0.01) decline in serum protein.However, co-administrated of *Matricaria chamomile* and *curcumin* extracts with Tetracycline appeared to be ameliorate te adverse effects of Tetracyclinee in renal function tests. On the other hand, histopathological examination of kidney sections of Tetracyclinee induction neprotoxic non treated showed marked attenuated the severity of Tetracycline nephrotoxicity, However, all these toxic effects were improved by administration of *Matricaria Chamomisle*or *curcumin* extract, but didn't bring them to the control limits. According to results the co-administration of *Matricaria chamomile* or *curcumin* with Tetracycline had beneficial effects on Tetracyclinee nephrotoxicity.

Key Words:- Nephroprotective, *Matricaria chamomile*, Curcumin, Albino rats, Histopathology.

INTRODUCTION

The kidney is well-known target of toxicity of therapeutic and ambient xenobiotics, due to its high blood flow, tubular transport processes and complex metabolic activities. (Ligha AE *et al*., 2015) explained that the kidneys are common organs affected by chemical toxicity. Where, the kidneys are responsible for the filtration of the blood, so many agents in the blood may accumulate there. However, it is a central organ which maintains homeostasis, regulating water and electrolyte balance and acid-base maintenance, among other crucial functions and also have an endocrine function (Ligha AE *et al*., 2009).

Though, nephropathy encountered widely among the peoples of the whole world, regardless of age, race, environmental and geographical distribution. The causes behind this complexity are a wide range of medicines caused different physiological disorders (Zhang FH *et al*.,

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1993). Over the past several years, the number of persons suffering from renal problems is increasing. The causes are: exposed to medicines, industrial/ environmental chemicals, age, pre-renal disease etc (Akram AE *et al*., 2014). A number of antibiotics include pencillin, Tetracyclinees, cephalosporines besides, aminoglycosides and sulfonamides are potential nephrotoxicants. The drug induced nephrotoxcicity is manifested functionally by decline urine concentration ampleness, tubular proteinurea, lysosomalenzymeurea, light glucosurea, sluggish ammonium excretion and declining glomerular infiltration rate (Anwar S *et al.*, 1999).

However, the most usual turbulence caused by Tetracyclinees is the exacerbating of azotemia caused by their impairment of amino acid incorporation into protein. Where, patients have precedence renal impairment are greater risk for Tetracyclinee toxicity and may sustain irreversible renal failure after receiving this antibiotic (Millier CS and Mcgarity GJ, 2009). So, Tetracyclinee should be avoided in such patient (Oyedeje KO *et al.*, 2013). Furthermore, No treatment is requiring except for cessation of the drug. Moreover, Tetracyclinee may cause dangerous sickness in patients with chronic renal failure (Bateman JC *et al.*, 1952; Womack CR *et al.*, 1952). For centuries, many herbs have been used as natural therapies for the forbiding and/or medicating of kidney diseases (Al-Snafi AE, 2015a, Al-Snafi AE, 2016b). Many previous studies showed that many herbs possessed reno-protective effects such as *Brassica nigra*and *Brassica rapa*(Al-Snafi AE, 2015_b), *Casuarinaequisetifolia* (Al-Snafi AE, 2015_c), *Citrulluscolocynthis* (Al-Snafi AE, 2016_b), *Clitoriaternatea* (Al-Snafi AE, 2016_c), *Coriandrumsativum*(Al-Snafi AE, 2016_d) and *Crocus sativus* (Al-Snafi AE, 2016e).

M. chamomile is one of the most widely used and well-documented medicinal plants in the world (Ragaa A, 2012). Chamomile, was used as plant medicine since the time of ancient Greece and Rome (Brown CB, 1971). There are numerous dissimilarities of chamomile but the most two folksy are Roman chamomile and German chamomile. German chamomile which is termed *Matricariachamomilla*, was considered the more potent of the two and took more scientific assessment (George CR, 1971). One hundred twenty chemical constituents have been recognized in chamomile, including terpenoids, flavonoids, and coumarins. It is used traditionally used (dried flower heads) as carminative, analgesic, and anticonvulsant in conventional remedy. Recent studies showed that it possessed anti-inflammatory vulnerary, deodorant, bacteriostatic, antimicrobial, carminative, sedative, some antimutagenic, cholesterol-lowering activities and antiseptic properties (Elkhamisy AE., 2015; Gescher *et al.*, 1998).

Curcumin, a safe nutritional component and a highly promising natural antioxidant with a detoxificant in several metal toxicity studies. However, Turmeric is a spice derived from the rhizomes of *Curcuma longa*, which is a member of the ginger family (Zingiberaceae). Curcumin, the principal curcuminoid found in turmeric, is generally considered the most active constituent (Kaloyanides GJ *et al*., 1980). However, other curcuminoids were isolated from turmeric include demethoxycurcumin and bisdemethoxycurcumin. In addition to its use as a spice and pigment. Curcumin, a yellow curry pigment from turmeric (*Curcuma longa*), was appeared to be a powerful anti-inflammatory, anti-cancer and anti-oxidant agent (Kamiya A *et al.*, 1983; Kawai Y *et al.*, 2005). It was documented from earlier studies that curcumin inhibited the development of pulmonary fibrosis (Kuchandy E *et al.*, 1990) and was used in inhibiting amiodarone-induced pulmonary fibrosis.

This study aims to evaluate the nephro-protective effects of (*M. chamomilla* and curcumin) in Tetracyclinee nephrotoxicity in rat model.

MATERIALS AND METHODS

Experimental animals

This study, carried out on 50 adult male albino rats of mean weight 200– 225 g. Their ages ranged from 10-14 weeks. The animals bring from the animal house, faculty of Science-Thi-Qar University/ Iraq. The animals were maintained in well ventilated cages under the prevalent weather conditions under 12-hour light/ dark cycle at a temperature of 22±2°C and healthy condition. Standard diet and water were given *ad libitum*. They were acclimatized to laboratory instances one week before the commencement of the experiments.

Matricaria chamomile and curcumin

Matricaria chamomilla, flowers and curcumin (turmeric) were purchased from a local bazaar-Attarine, Al-Basra, Republic of Iraq, Then they were extracted by distilled water, dried and stored till their use.

Drug

Tetracyclinee hydrochloride (Actavis, Barnstaple, EX32, UK). Two hundred and fifty milligram (250 mg) of Tetracyclinee was dissolved in 10 ml of distilled water to give a concentration of 25 mg/ml.

Experimental Design

The experiment animals were divided in 6 groups (6 rats each), and designed as following:

Group 1 (Control): Rats were received distilled water IP in a dose of 1 ml/kg BW for 14 days as a negative control.

Group 2 (Induction); Rats were received Tetracyclinee in a dose of 25 mg/ kg BW IP for 14 days and treated by distal water as a positive control (Oyedeji KO *et al.,* 2013).

Group 3: Rats were received *M. chamomilla extract* by gastric gavage (50 mg/kg BW.).

Group 4: Rats were co-treated *M. chamomilla extract* with Tetracyclinee for 14 days (Akram R, *et al.,* 2014).with one hour in between.

Group 5: Rats received Curcumin 200mg/kg BW Daily for 14 days (Mohamed R; 2015).

Group 6: Rats were co-treated by curcumin with Tetracyclinee for 14 days as treated groups. with one hour in between.

At the end of the experimental interval, the rats were fasted over night. In the next day the animals were anesthetized by ether, and blood samples were collected by direct heart puncture, samples were centrifuged at 3500 rpm for 10 minutes. Sera were frozen until used for the biochemical assays.

Biochemical assays

At the end of the experiment on the 14^{th} day, the animals were stayed overnight. The next morning (on the 15^{th} day), blood samples were took for serum creatinine (mg/dl), total protein (mg/dl) urea(mg/dl), Sodium (Na) (mmol/L and Potassium (K) (mmol/L). Increasing of urea and creatinine level in the serum was taken as an indicator of nephrotoxicity (Anwar A, 1999).

The serum parameters were analyzed spectrophotometrically by using double beam UV Visible spectrophotometer (UV-Visible spectrophotometer, Elico, model SL 150). However, evaluation of blood urea, and creatinine were carried out using peculiar diagnostic kits bought from Transasia Bio-medicals Ltd (HP) in collaboration with Erba diagnostics Mannheim GmbH (Germany) according to the methods of Talke and Schubert *et al* respectively. Sodium (Na) and Potassium (K) analysis were accomplished by Excel diagnostic kit method according to the method of (Terri AE *et al.,* 1958).

Histopathological examination

The kidney's specimens of sacrificed animals were distincted and accurately dissected out for histopathological examination, thereafter were fixed in a 10% neutral buffered formaldehyde solution. After routine processing the tissue specimens were embedded in paraffin wax and sectioned (thickness, 4-5 µm). The sections were stained with hematoxylin and eosine (H&E). Histopathological evaluation of the H&E- stained section was checked with Olympus light microscope.

Statistical Analysis

Statistical analysis of was performed by paired students t-test, using computerized SPSS program (Statistical Package for the Social Sciences. Differences were considered significant at $P<0.05$. (Sabin L and Everit S, 2004).

RESULTS

In the current study, the effects of *M. chamomilla* and curcumin aqueous extracts on rats biochemical components of the serum of nephrotoxic rats induced by Tetracyclinee chloride were depicted in Tables (1) and the histological effects were shown in Figure1. Tetracycline chlorides administration caused significantly increment in all kidney function standards (serum urea, total protein, serum K and Na) investigated in this study compare with control group. On the other hand, co-treatment with *M. chamomilla* and curcumin extract showed good reno-protective effects via attenuation of the elevated serum parameters. However, *curcumin* with Tetracycline provided the better protection than *M. chamomilla* extract by attenuating the elevated level of total protein, urea, creatinine and K^+ compared with untreated group. Nonetheless, the results revealed that both treatment were not affected serum Na^+ level significantly.

Experimental animals received distal water showed normal structure of kidney with intact Bowmans capsule and convoluted tubules. The kidney tissue sections of Tetracycline-treated animals declared noticeable histopathological changes, including tubular epithelial necrosis, epithelial cell degeneration, break down of glomerular capillaries and vacuolar emergence in tubular lumen, with granular eosinophilic materials in some lumen tubules. Epithelial desquamation, atrophic glomeruli effected most of the cortical zone. Additionally, the section showed infiltration of inflammatory cells (lymphocytes, neutrophils, and fibroblasts), peritubular and glomerular congestion, tubular casts, interstitial edema, blood vessel congestion which represented the features of tubular necrosis. In contrast, the treatments (*M. chamomile* and curcumin extracts) provided protection

against Tetracycline-induced nephrotoxicity. Significant alleviation in the cellular infiltrates, vascular degeneration of tubular epithelial cells, no glomerular congestion, no tubular casts, only peritubular congestion, no tubular casts, or epithelial desquamation, only peritubular edema were observed in the kidney morphology compared to the Tetracycline-treated animals(Figure1;a,b,c,d,e,f).

Table 1. Nephroprotective Effect of *M. chamomile* and *curcumin* aqueous extracts in Tetracycline- induced renal damage, compared to un-treated rats. The values were expressed as mean ± SD.

Groups	Parameters				
	Creatinine (mg/dl)	Serum urea(g/dl)	Total(protein (g/dl)	K^+ (mmol/L)	Na^+ (mmol/L)
G1	0.42±0.08	27.35± 1.82	5.75± 0.01	5.61±0.66	129.62±0.23
G2	0.67± 0.07[a]	54.9± 1.23[a]	3.88±0.49[b]	11.23±0.81[a]	121.09±3.45[a]
G3	0.43 ± 0.15 [NS]	26.60 ± 1.82 [NS]	4.71 ± 1.20 [NS]	6.01±0.16 [NS]	130.32±0.13 [NS]
G4	0.60±0.05[b]	44.09±0.09[b]	3.88±0.49[b]	9.23±2.12[b]	123.33±0.99 [NS]
G5	0.40 ± 0.04 [NS]	27.33 ± 0.92 [NS]	5.05 ± 1.04 [NS]	4.64±0.55 [NS]	130.01±0.11 [NS]
G6	0.52±0.09[c]	35.11±0.08[c]	4.06±0.13[b]	8.09±1.89[b]	124.34±1.02 [NS]

[a]p<0.01, [b]p<0.01 and [c]p<0.001, [NS]: not significant compared with untreated group.

Fig 1. Histopathological features

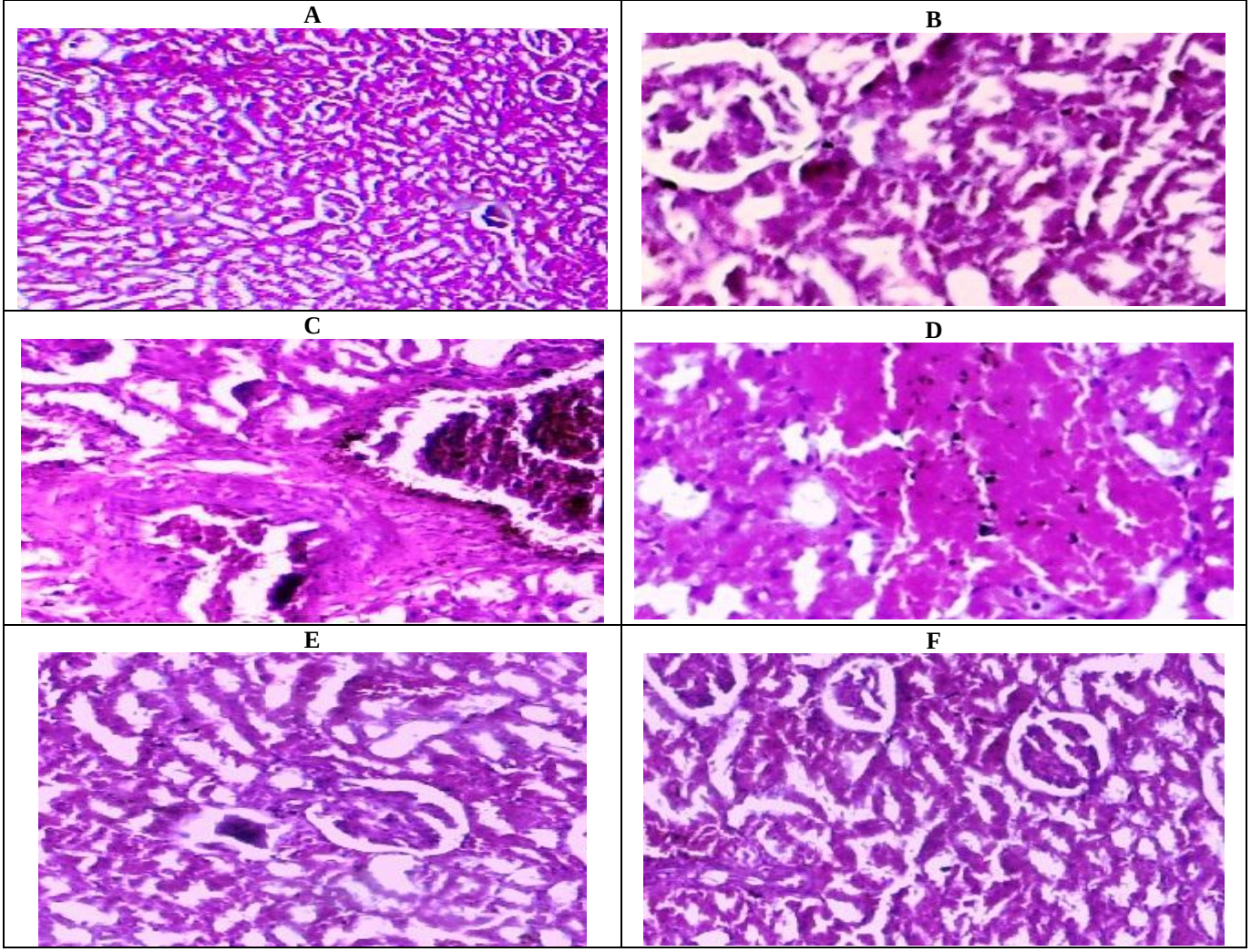

Fig.1(A,B,C,D): Histopathological features showed the effect of *M. chamomile* and curcumin aqueous extract on tetracycline- induced nephrotoxicity in rats. (A) Kidney tissue section of control animals showed the normal histopathological structure of renal parenchyma (x200). (B) Light cystic dilatation of some renal tubules, Epithelial cells desquamtion, break down of glomerular tuft and vacuolar emergence of endothelial lining, glomerular tufts as well as epithelial lining renal tubules is noticed (x400). (C) Kidney of rat from group 2 showed that the tetracyclin-treated animals had an abnormal collagen deposition (fibrosis), sever degenerative changes and distorted kidney morphologies Additionally, there were infiltration of inflammatory cells, peritubular and glomerular congestion, tubular casts, interstitial edema, which represented the features of tubular necrosis (x400). (D) homogenous eosinophilic masses in the lumen. Some renal tubules showed pressure atrophy. Furthermore, the tubules epithelia infiltrated by few inflammatory cells (x400).(E-F) kidney sections of rats from G4 & G6, co-treated animals with *M. chamomile* extract and *curcumin* with tetracycline showed reduced collagen depositions, reduced renal tubular thickening, minor collagen deposition, decline in the cellular infiltrates and thin-interstitial septa (x400).

DISCUSSION

The present study was undertaken to accomplish the effect of *M.chamomilla* and curumin aqueous extracts on the renal function parameters (creatinine, urea and total protein). Previous researches showed that Tetracycline which used extensively as antimicrobial drug, it was not free from side effects (Li X *et al.,* 2011). However, renal toxicity, rise in BUN has been reported and is apparently dose related with Tetracyclinee, but do not necessarily guide renal dysfunction (Reddy J, 1981). Histopathological changes associated with Tetracycline in this study were also similar to that documented by many researchers **(**Bihorac *et al.,* 1999**;** Bihorac I *et al.,* 1999). Patients who are suffering from pre-renal Tetracyclinee deficit may develope azotemia, hyperphosphatemia, and acidosis. Patients with dehydration are more susceptible (Brown CB, 1971).

In this study, creatinine and urea levels were increase in Tetracycline-treated group compared to control group. The increment in urea and creatinine level was previous mentioned (Weichert KJ *et al.,* 1999; Yanardag H *et al.,* 2005; Miller CS and McGarity GJ, 2009). Their elevation was the early-impaired renal function and renal tubular damage (Kawai Y *et al.,* 1999. The biochemical standards such as blood urea, total protein and creatinine levels as well as electrolytes as K^+ and Na^+ were usually used to emphasize drug-induce nephrotoxicity in animals and man (Sahoo HB *et al*., 2012). However, the results demonstrated that the Tetracycline nephrotoxicity was associated with significant ($p<0.01$ and $p<0.001$ respectively) elevitations in the levels of blood urea and serum creatinine as well as significant ($p<0.01$) decrease in the levels of total protein, electrolytes K^+ and Na^+.

However, those changes were attenuated in groups received Tetracycline with *M. chamomilla or curcumin*, they significantly lowered the blood urea, blood creatinine, sodium and potassium level and elevated the total protein when compared with the untreated group. These effects were further confirmed by histological effects of both treatments. The nephroprotective activity of extracts could be attributed to their antioxidant activity. The efficacy of *Curcuma longa* and *Matricaria chamomilla* as nephroprotective was is agreement with many previous studies (Morsy *et al.,* 2013; Najla *et al.,* 2012). The nephroprotective effect of *Curcuma longa* might be attributed to its antioxidant and/ or free radical scavenging activity. Furthermore, they might be potentially useful in kidney diseases by preventing renal inflammation which represent the initial step in neprotoxicity (Rekka EA *et al.,* 1996; Zhong FH *et al.,* 2011).

CONCLUSION

From the results of current study we can concluded extracts of *M. chamomilla* and *curcumin* possessed renoprotective effects in Tetracycline-induced nephrotoxicity in rats when used simultaneously with Tetracycline, this effect could be attributed to their antioxidant effects, They could be exert similar influences in human. As a result of effectiveness, safety and availability, they represented good alternatives for the using of chemical drugs.

Fig 1(A,B,C,D) Histopathological features showed the effect of of *M. chamomile* and curcumin aqueous extract on Tetracycline-induced nephrotoxicity in rats. (A) Kidney tissue section of control animals showed the normal histopathological structure of renal parenchyma (x200). (B) Light cystic dilatation of some renal tubules, Epithelial cells desquamtion, breakdown of glomerular tuft and vacuolar emergence of endothelial lining, glomerular tufts as well as epithelial lining renal tubules is noticed (x400). (C) Kidney of rat from group 2 showed that the Tetracycline-treated animals had an abnormal collagen deposition(fibrosis), sever degenerative changes and distorted kidney morphologies Additionally, there were infiltration of inflammatory cells, peritubular and glomerular congestion, tubular casts, interstitial edema, which represented the features of tubular necrosis

(x400). (D) homogenous eosinophilic masses in the lumen. Some renal tubules showed pressure atrophy. Furthermore, the tubules epitheliain filtrated by few inflammatory cells(x400).(E-F) kidney sections of rats from G4 & G6, co-treated animals with *M. chamomile* extract and *curcumin* with Tetracycline showed reduced collagen depositions, reduced renal tubular thickening, minor collagen deposition, decline in the cellular infiltrates and thin-interstitial septa (x400).

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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