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Role of Cinnamon Extract in the Protection Against Co-amoxiclav-Induced Nephrotoxicity Damage in Male Albino Rats

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ABSTRACT

Co-amoxiclav (CA), which is effectively used in the treatment of several number of bacterial infections, may cause nephrotoxicity. Cinnamon extract contains natural products which showed antioxidant, anti-inflammatory and anti-bacterial properties. In the present study, two doses of CA, therapeutic (30 mg/kg) and double therapeutic (60 mg/kg), were orally given to rats alone or in combination with cinnamon (200 mg/kg) for 10 consecutive days, to test the potential protective impact of cinnamon extract against CA-induced nephrotoxicity. Obtained results showed significant increases in serum concentration of creatinine (Cr), urea (Ur) and uric acid (UA) in rats treated with CA. Renal contents of malondialdehyde (MDA), protein carbonyl (PC), hydrogen peroxide (H_2O_2) and nitric oxide (NO) were also markedly increased following administration of CA. On contrary, treatment with CA produced significant decreases in the renal levels of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRd), glutathione-s-transferase (GST) and reduced glutathione (GSH). The drug was also found to induce up regulation of pro-apoptotic p53 and caspase-3 proteins expression, while it down regulated the expression of the anti-apoptotic protein Bcl-2 in the kidney of treated rats. CA-induced adverse effects in all investigated biochemical indices seemed to be dose-dependent. However, administration of cinnamon extract along with CA to rats reduced renal injury, oxidative stress and apoptosis caused by treatment with CA alone. It could be concluded that cinnamon extract may be useful in the protection against CA-induced renal damage in rats.

1. INTRODUCTION

Amoxicillin is a semi-synthetic penicillin (Fig. 1), which has been effectively used as antibiotic in the treatment of various bacterial infections. It possesses a potent anti-bacterial effect against all of gram negative as well as most of the gram-positive bacteria (Finlay2003). The drug has been combined with clavulanic acid (Fig. 1), an inhibitor of bacterial 3-lactamases, to decrease antimicrobial resistance (Labia 1978& Larrey1992).

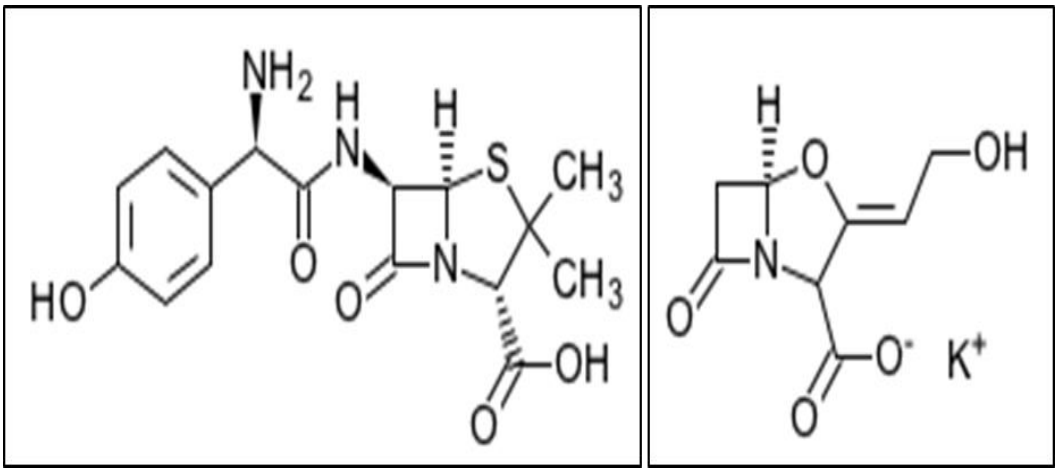


Figure 1: Chemical structure of amoxicillin and clavulanic acid.

Kidney, as a primary organ which eliminates the exogenous drugs and toxins, may represent a target organ for the adverse effects of these chemicals which may cause disturbance in the renal function and hence nephrotoxicity (Perazella2009 & Barnett 2018). Published data provided evidence that CA is one of the drugs, which can induce nephrotoxicity (Vodovar, 2018). The drug may further cause renal failure in the rats which was characterized by Co-amoxiclav induced nephrotoxicity seems to be due to induction of oxidative stress. In previous animal studies, CA was found to produce increase in the levels of lipid peroxidation product (MDA) and decrease in both glutathione (GSH) contents and antioxidant enzymes activities in both liver and kidney (El-Hosseiny2016 & Altin2017). A major issue in therapy with many drugs is the potential side effects and toxicity of these synthetic chemicals to normal tissues. For this important reason, there is an urgent need to identify safe agents with potentiality to prevent or reduce the adverse effects induced by drugs. In recent years, plants and their extracts have been thoroughly investigated for their biological and medicinal activities (Atanasov 2015). Many of these extracts were found to exert therapeutic and protective effects against different diseases and drugs or toxins-induced toxicity (ElKady2016& Berman2017). Cinnamon (Cinnamomum zeylanicum) is a tropical evergreen tree belonging to the family Lauraceae. The bark of various cinnamon species is one of the most important and popular spices used worldwide for both cooking, and traditional and modern medicines (Vangalapati 2012). Cinnamon has strong neuroprotective, hepatoprotective, cardioprotective and gastroprotective effects due to its potent antioxidant and anti-inflammatory properties (Mathew 2006&Vangalapati 2012). The antioxidant activity and the beneficial health effects of cinnamon bark is attributed to the presence of polyphenolic component like proanthocyanidins (Peng 2008). Furthermore, cinnamon extract exerted anti-apoptotic effect through modulating the changes in apoptotic markers induced by chemicals such as cisplatin. (ElKady2016). On the other hand, cinnamon and its oils, like CA, showed anti-bacterial activity (Nabavi 2015). Based on the ability of cinnamon to exert antioxidant, anti-inflammatory and anti-bacterial actions, this study was undertaken to examine, the potential protective impact of ethanolic extract of cinnamon bark against CA-induced nephrotoxicity in male albino rats.

2. METHOD

1. Animals Forty-two healthy male Wistar rats weighing 150-170 g were used. They were obtained from animal house of the Biological Products & Vaccines (VASERA), Cairo, Egypt. Rats were left for two weeks for acclimatization before starting the experiment. They were kept in plastic cages, fed on basal diet and given water ad-libitum. All care and procedures adopted for the present investigation were accordance to the approval of animal ethics committee of Mansoura University, Egypt.

2. Co-amoxiclav (CA) which composed of Amoxicillin/clavulanic acid (625mg) was purchased from local pharmacy at Mansoura city, Egypt in the form of film-coated tablets manufactured by GlaxoSmithKline®. The tablets were grinded till forming powder, then suspended in distilled water (w/v). Drug suspension then was given daily to the rats according to the selected doses (30 and 60mg/kg).

3. Preparation of cinnamon extract Cinnamon barks were purchased from local aromatherapy market at Mansoura city, Egypt. The cinnamon barks were washed well, dried and about 100 g was grinded to form powder. The powder of cinnamon barks was extracted with 2 liters of 70% ethanol in bottle for 72 hours. The extract solution was filtrated and the solvent (ethanol) then was evaporated at room temperature for 5 days extract.
The residues of extract was collected, weighted and dissolved in DMSO (10%). The solution was then kept in refrigerator and given daily to the rats using gastric tube in a dose of 200 mg/kg.
4. Experimental design After two weeks of acclimatization, rats were divided randomly into seven groups of six rats per each, as follows: group (1) control; group (2) DMSO 10%; group (3) cinnamon extract, 200 mg/kg (Shokri 2015); group (4) CA30, 30 mg/kg (El-Hosseiny2016); group (5) CA30+cinnamon, as groups 3 and 4; group (6) CA60, 60 mg/kg; and group (7) CA60+cinnamon, as groups 3 and 6.
All chemical solutions used for treatment were introduced to rats by gavage once a day for 10 days. At the end of the experiment, overnight fasted rats were anesthetized by ketamine/xylazine (10 ml/kg, ip), and blood samples were collected by cardiac puncture using vacuum tubes. The tubes were then centrifuged at 3000 rpm for 20 min to separate sera which were labeled and kept at -20 0C until biochemical analysis. Tissue samples were obtained from the right lobe of the liver cleaned, weighed and stored at -20 °C. Later, tissue samples were removed from deep freezer and homogenized in normal saline to form 10% (w/v), and the homogenates were centrifuged (1000 rpm) for 5 min to separate the supernatant which used for biochemical assays.
5. Biochemical investigations The level of kidney malondialdehyde (MDA) was measured by the method of Ohkawa 1979. Kidneycontent of PC was determined according to the method described by Dalle-Donne2003. Kidney content of H2O2 was estimated by the method of Aebi 1984. Level of NO in Kidney tissue was determined on the basis of procedure of Montogomery 1961. The concentration of GSH in the Kidney was estimated by the method of Beutler1963. Activities of SOD, CAT, GPx, GRd and GST in the Kidney were evaluated by the methods of Nishikimi 1972, Aebi 1984, Paglia 1967, Goldberg 1983 and Habig 1974 respectively.
Activities of Cr, Ur, and UA in serum were estimated following to methods described by Fossati 1983, Young 2001 and Young 2001. Renal apoptotic markers p53, caspase-3 and Bcl-2 were evaluated by flow cytometric analysis according to the method reported by Gong 2007.
6. Statistical analysis Differences among groups were evaluated by one-way analysis of variance (ANOVA) followed by Duncan's multiple range tests. All values were expressed as mean ± SE, and p-values equal or less than 0.05 were considered significant.

3. ETHIC APPROVAL

healthy male Wistar rats weighing 150-170 g were used. They were obtained from animal house of the Biological Products & Vaccines (VASERA), Cairo, Egypt. Rats were left for two weeks for acclimatization before starting the experiment. They were kept in plastic cages, fed on basal diet and given water ad-libitum. All care and procedures adopted for the present investigation were accordance to the approval of animal ethics committee of Mansoura University, Egypt..

4. RESULT

Table (1) shows that, treatment of male rats with CA in doses of 30 and 60 mg/kg for 10 consecutive days caused dose-dependent significant increases in the activities Cr, Ur, and UA in the serum, as compared to control group. However, treatment with cinnamon extract (200 mg/kg) along with CA for the same period led to reduce elevated serum levels of measured biomarkers of kidney injury, as compared to CA-treated groups alone.
In table (2), treatment of rats with CA (30 and 60 mg/kg) produced dose-dependent significant increases in the renal content of MDA, PC, H2O2 and NO, in comparison with results of control group. Meanwhile, combined treatment with cinnamon extract and CA(30 and 60 mg/kg) significantly lowered the raised renal concentrations of MDA, PC, H2O2 and NO, when compared to AC-treated groups alone.
As described in table (3), renal levels of GSH, SOD, CAT, GPx, GRd and GST were markedly decreased, in a dose-dependent manner, in rats administered CA, in comparison with control. In rats treated simultaneously with cinnamon extract and CA, the activity of mentioned antioxidant enzymes along with the level of GSH in the kidney were markedly elevated, in comparison with groups treated with CA alone.

Table (4) and figure (2) exhibit that, treatment of male rats with CA (30 and 60 mg/kg) for 10 consecutive days caused dose-dependent marked increases in the pro-apoptotic protein's expression p53 and caspase-3, accompanied with a significant decrease in the anti-apoptotic protein Bcl-2, as compared to control group. However, combined treatment with cinnamon extract and CA displayed remarkable reduction in the proapoptotic proteins expression caspass-3 and p53, parallel to marked increase in the anti-apoptotic protein Bcl-2, in comparison with results of rats administered CA alone.

It has been noticed that, treatment with cinnamon extract alone or DMSO alone had no significant adverse effects on all investigated parameters (Tables 1, 2 and 3).

Table 1: Effect of cinnamon extract on CA-induced adverse changes in the kidney injury markers in male rats.

		C	DMSO	Cin	CA 30	Cin + CA 30	CA 60	Cin + CA 60
Cr (mg/dl)	Mean ± SE	0.45 ± 0.02	0.45 ± 0.03	0.45 ± 0.02	0.93 ± 0.02^{A}	0.55 ± 0.03^{AB}	1.24 ± 0.02^{A}	0.65 ± 0.04^{AC}
Urea (mg/dl)	Mean ± SE	28.88 ± 1.98	29.53 ± 1.32	27.76 ± 1.52	59.40 ± 2.22^{A}	36.08 ± 1.27^{AB}	67.43 ± 2.21^{A}	40.9 2±1.84^{AC}
Uric acid (mg/dl)	Mean ± SE	2.18 ± 0.04	2.19 ± 0.04	2.16 ± 0.03	5.04 ± 0.08^{A}	2.79 ± 0.20^{AB}	5.97 ± 0.20^{A}	2.97 ± 0.17^{AC}

- C = Control, DMSO = Dimethylsulfoxide, Cin = Cinnamon, CA = Co-amoxiclav.
- Values were expressed as mean ± SE (n = 6 for each group).
- a, b and c = Significantly difference at $p \leq 0.05$ comparing to control, CA 30 mg and CA 60 mg respectively.

Table 2: Effect of cinnamon extract on CA-induced deleterious changes in markers of oxidative tissue damage in the kidney of male rats.

		C	DMSO	Cin	CA 30	Cin + CA 30	CA 60	Cin + CA 60
MDA (nmol/g	Mean ± SE	42.99 ± 1.88	43.23 ± 1.96	42.58 ± 2.37	89.27 ± 2.42^{A}	51.25 ± 2.44^{AB}	114.0 ± 4.26^{A}	58.80 ± 2.64^{AC}
PC (nmol/g)	Mean ± SE	17.19 ± 0.75	17.06 ± 0.67	16.56 ± 0.67	40.10 ± 1.53^{A}	19.95 ±0.48^{AB}	55.56 ± 1.04^{A}	21.54 ± 0.72^{AC}
H_2O_2 (mM/g)	Mean ± SE	10.58 ± 0.69	10.23 ± 0.67	10.12 ± 0.41	38.31 ± 1.48^{A}	14.24 ± 0.82^{AB}	51.86 ± 1.83^{A}	14.72 ± 0.44^{AC}
NO (µmol/g)	Mean ± SE	48.95 ± 0.81	42.95 ± 1.61	43.84 ± 1.70	74.14 ± 1.75^{A}	51.38 ±0.46^{AB}	86.02 ± 2.13^{A}	53.90 ±0.80^{AC}

- C = Control, DMSO = Dimethyl sulfoxide, Cin = Cinnamon, CA= Co-amoxiclav.
- Values were expressed as mean ± SE (n = 6 for each group).
- a, b and c = Significantly difference at $p \leq 0.05$ comparing to control, CA 30 mg and CA 60 mg respectively.

Table 3: Effect of cinnamon extract on CA-induced adverse changes in antioxidant parameters in the kidney of male rats.

		C	DMSO	Cin	CA 30	Cin + CA 30	CA 60	Cin + AC 60
SOD (U/L)	Mean ± SE	38.12 ± 1.39	38.27 ± 0.96	40.98 ± 1.02	16.20 ± 1.06^{A}	30.65 ± 1.01^{AB}	11.48 ± 0.68^{A}	28.59 ± 0.95^{AC}
CAT (U/L)	Mean ± SE	67.03 ± 1.38	66.92 ± 1.04	67.43 ± 1.07	35.11 ± 1.55^{A}	60.28 ± 1.71^{AB}	28.34 ± 1.14^{A}	58.05 ± 2.09^{AC}
GSH (MG/G)	Mean ± SE	7.32 ± 0.10	7.25 ± 0.10	7.47 ± 0.09	4.09 ± 0.14^{A}	6.63 ± 0.21^{AB}	3.37 ± 0.22^{A}	6.34 ± 0.21^{AC}

- C = Control, DMSO = Dimethyl sulfoxide, Cin = Cinnamon, CA = Co-amoxiclav.
- Values were expressed as mean ± SE (n = 6 for each group).
- a, b and c = Significantly difference at $p \leq 0.05$ comparing to control, CA 30 mg and CA 60 mg respectively.

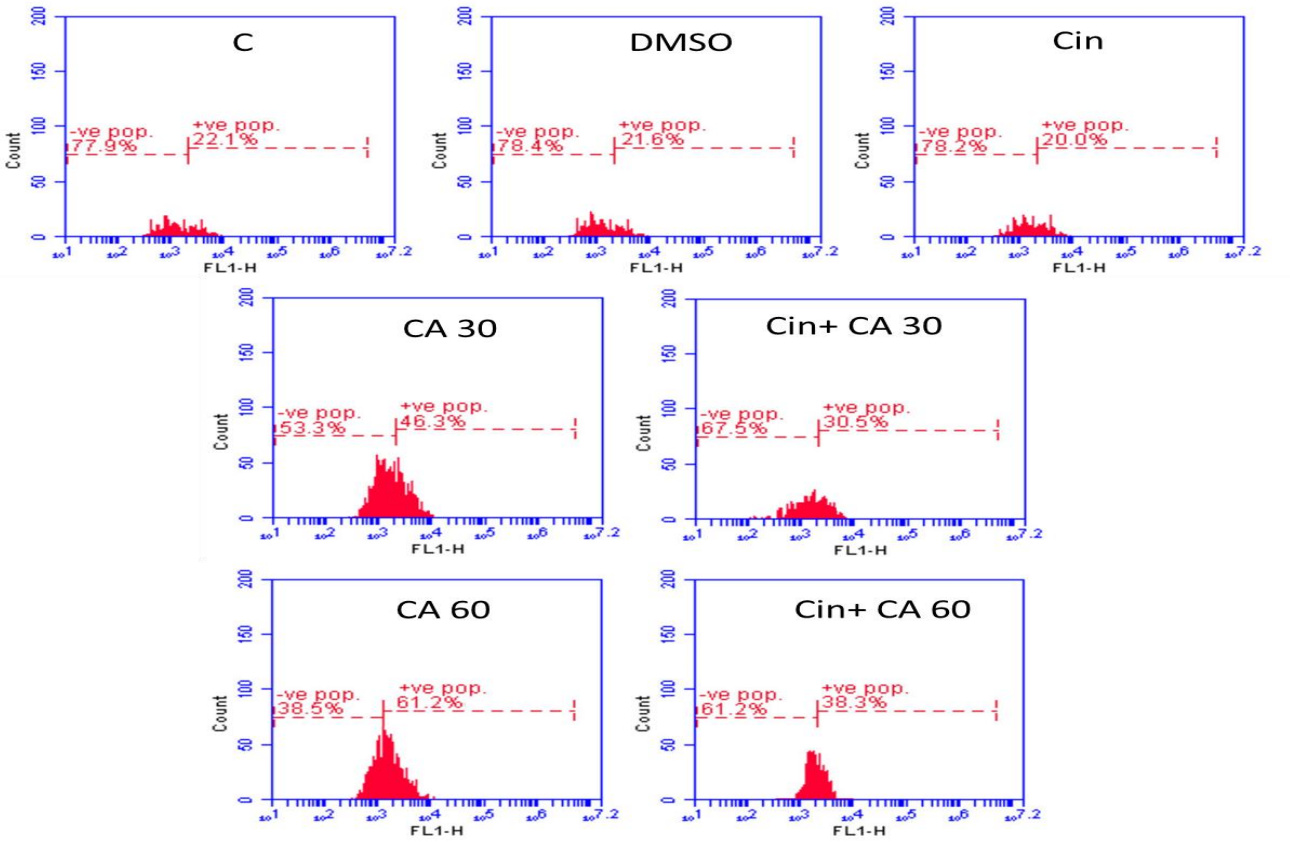
		C	DMSO	Cin	CA 30	Cin + CA 30	CA 60	Cin + CA 60
GPx (U/G)	Mean ± SE	60.53 ± 1.50	60.07 ± 1.87	61.10 ± 1.44	36.32 ± 0.57^{A}	51.03 ± 1.47^{AB}	26.01 ± 1.68^{A}	48.75 ± 1.21^{AC}
GR (U/G)	Mean ± SE	7.01 ± 0.12	7.05 ± 0.09	7.11 ± 0.07	4.42 ± 0.07^{A}	6.21 ± 0.28^{AB}	2.89 ± 0.05^{A}	6.18 ± 0.15^{AC}
GST (U/G)	Mean ± SE	68.40 ± 1.31	68.34 ± 1.39	68.47 ± 1.38	28.47 ± 1.46^{A}	60.17 ± 1.35^{AB}	18.88 ± 0.99^{A}	57.32 ± 1.75^{AC}

- C = Control, DMSO = Dimethylsulfoxide, Cin = Cinnamon, CA = Co-amoxiclav.
- Values were expressed as mean ± SE (n = 6 for each group).
- a, b and c = Significantly difference at $p \leq 0.05$ comparing to control, CA 30 mg and CA 60 mg respectively.

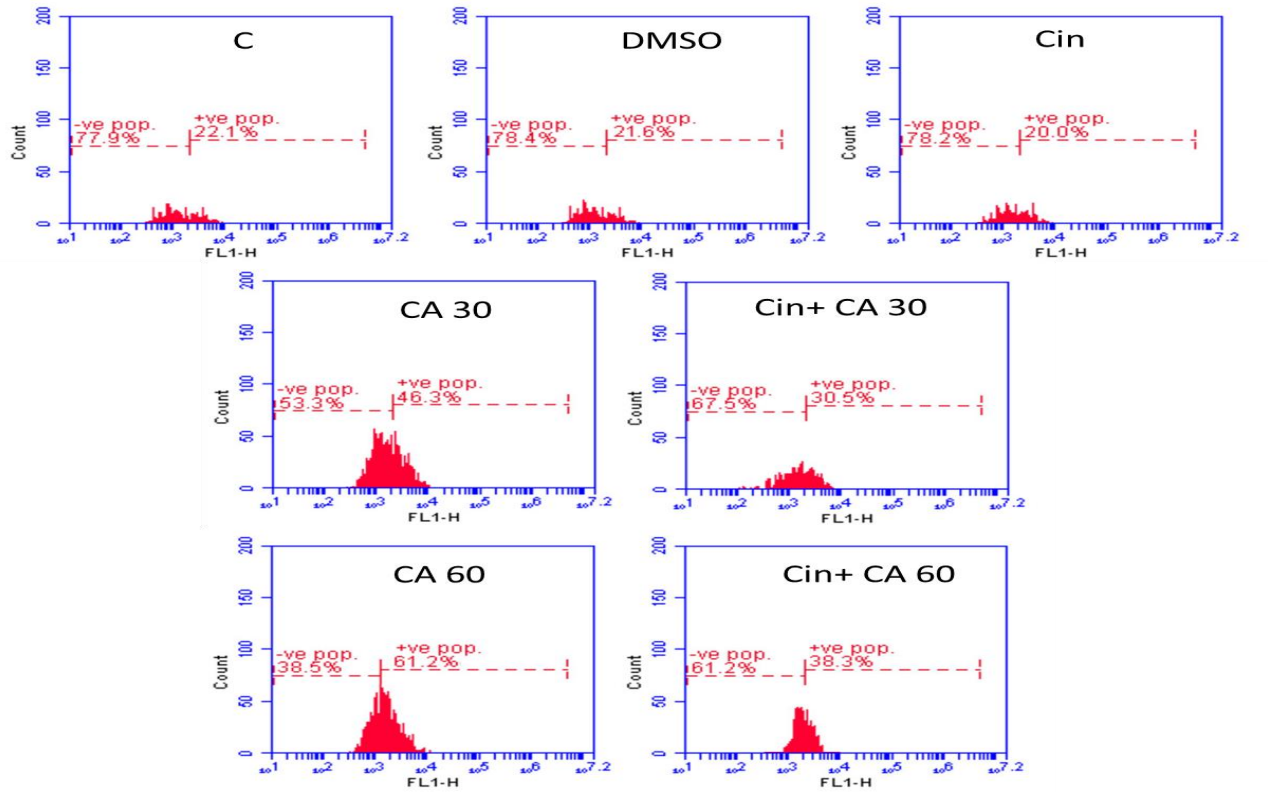
Table 4: Effect of cinnamon extract on CA-induced apoptosis in the liver of male rats.

		C	DMSO	Cin	CA 30	Cin + CA 30	CA 60	Cin + CA 60
Bcl2 (%)	Mean ± SE	83.67 ± 1.63	83.13 ± 0.79	83.90 ± 1.83	41.10 ± 1.87^{A}	72.73 ± 2.40^{AB}	31.40 ± 0.69^{A}	64.93 ± 2.15^{AC}
	*		-0.65	+0.27	-50.88	-13.08	-62.47	-22.39
	**					+76.95		
	***							+106.78
Caspase-3 (%)	Mean ± SE	31.37 ± 1.49	30.97 ± 1.11	30.57 ± 0.62	56.07 ± 1.32^{A}	40.23 ± 1.39^{AB}	66.43 ± 1.59^{A}	48.50 ± 1.46^{AC}
	*		-1.28	-2.55	+78.73	+28.24	+111.76	+54.61
	**					-28.25		
	***							-38.97
P53 (%)	Mean ± SE	22.67 ± 1.39	21.80 ± 1.11	21.37 ± 0.69	47.20 ± 1.96^{A}	32.40 ± 1.75^{AB}	61.20 ± 1.85^{A}	39.90 ± 2.50^{AC}
	*		-4.21	-5.73	+108.20	+42.92	+169.96	+76.00
	**					-31.36		
	***							-34.80

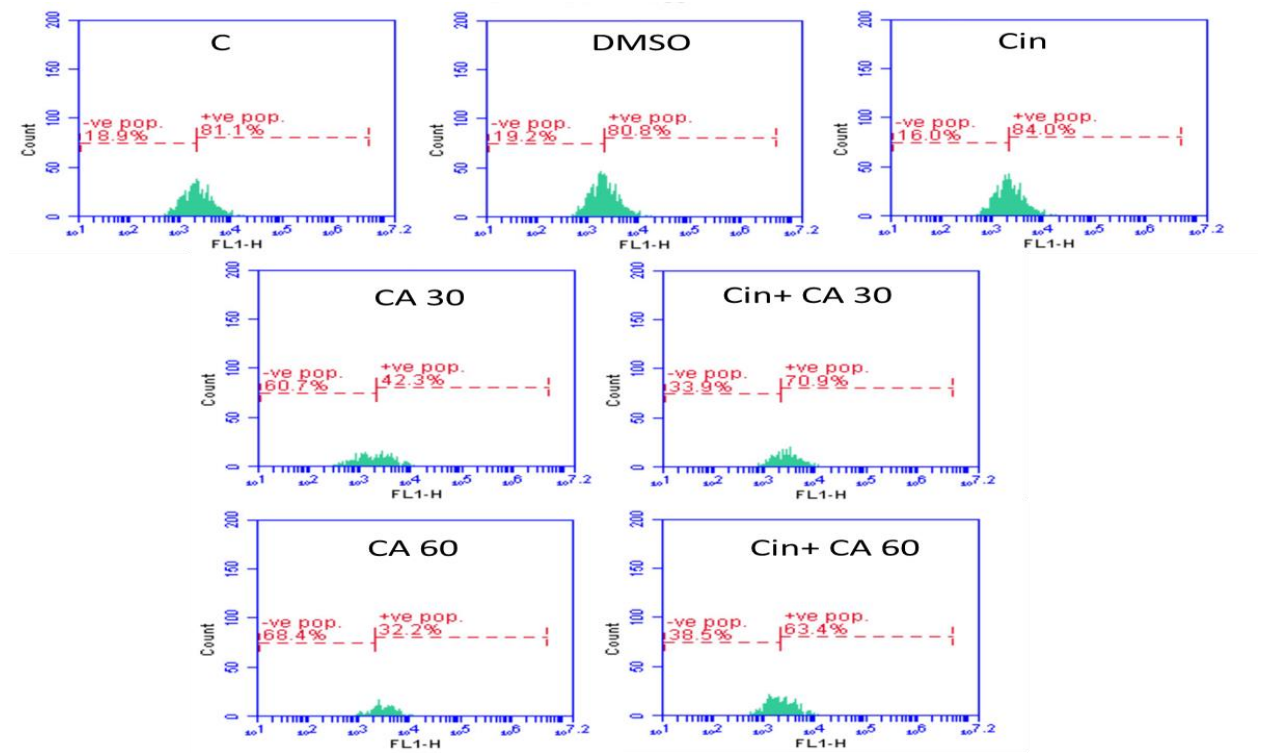
- C = Control, DMSO = Dimethylsulfoxide, Cin = Cinnamon, CA = Co-amoxiclav.
- Values were expressed as mean ± SE (n = 6 for each group).
- a, b and c = Significantly difference at $p \leq 0.05$ comparing to control, CA 30mg and CA 60mg respectively



Flow cytometry chart showing examples of data generated by BD Accuri™ C6 for determination of p53 in kidney of different animal groups.



Flow cytometry chart showing examples of data generated by BD Accuri™ C6 for determination of caspase-3 in kidney of different animal groups.



Flowcytometry chart showing examples of data generated by BD Accuri™ C6 for determination of Bcl-2 in kidney of different animal groups.

5. DISCUSSION

The present study also aimed to examine the nephrotoxicity of two oral doses of CA, one therapeutic (30 mg/kg) and the other double therapeutic (60 mg/kg) for 10 days in male wistar rats. The results of the present study indicated that oral administration of CA at doses of 30 and 60 mg/kg/day for 10 days induced significant renal impairment in male rats. Available literature on CA nephrotoxicity revealed several different doses of CA required to induce renal impairment. For example, 7used a dose of 21.83 mg/kg (twice daily) of CA in adult male Wistar rats for 7 days and found that it produced several signs of nephrotoxicity. Also, Olayinka 2012 reported that CA in male rats when given orally (14.25 mg/kg and 21.83 mg/kg) twice a day for 7 days produced severe renal impairments. In this work, treatment of rats with CA treated rats alone (30 mg/kg or 60 mg/kg) for 10 days produced dose dependent significant increases in serum Cr, UA and Ur levels, indicating impaired renal function. Such impairment may be attributed to renal insufficiency perhaps due to oxidative tissue damage. In similar study, Ur has been reported to increase in acute and chronic intrinsic renal disease (Carvounis 2002). In addition, Ginès 2013 observed significant increase in serum Cr in animal or human after treatment with the drug.

Although the mechanisms by which CA induced nephrotoxicity are not fully understood, implication of oxidative stress has been suggested. However, development of CA-induced renal injury may be resulted from the production of free radicals which initiate the process of LPO leading ultimately to membrane damage, kidney failure and protein oxide (Deavall 2012). In accordance, the present data showed that CAcan cause oxidative stress in the kidney of rats as showed by dose-dependent significant increases in the renal content of MDA, PC, H_2O_2 and NO. Since MDA is a product of free radical-induced LPO, thus it represents a marker of injury of cell due to oxidative stress (Ayala 2014).

In this regard 30 found that treatment of rat with different doses of CA (14.25 mg/kg and 21.83 mg/kg) twice for seven days produced LPO in the liver and kidney tissue.

Overproduction of NO is toxic to the cell (Iwakiri 2015)**,** this is because NO acts as a pro-inflammatory mediator which can induce inflammation in abnormal conditions (Sharma 2007). In the present study, treatment with CA in adult rats produced dose-dependent marked increase in the renal content of NO. This finding suggested that kidney may produce an inflammatory response as a part of its mechanism of cytotoxicity. Thus, oxidative stress and inflammation play a crucial role in CA-induced nephrotoxicity. It is worthwhile to mention that, NO can cause serious oxidative stress and cell death by its combination with superoxide anion (O2·-) which results in generation of peroxynitrite (ONOO-) that can oxidize DNA bases, proteins, lipids and thiol groups (Meguro 2003& Abdelmegeed 2014).

Induction of oxidative stress by CA in the current study could reflect disturbance of cellular antioxidant system that detoxifies free radicals and ROS. Obtained results demonstrated dose-dependent marked decreases in the renal level of GSH and activity of antioxidant enzymes including SOD, CAT, GPx, GR and GST in rats treated with CA. This result together with the increased oxidant products (MDA, PC and NO) in the kidney indicated that CA induced oxidative stress in the treated rats.

In effect, GSH is considered one of the most effective cellular non-enzymatic antioxidants in the body. It is a redox molecule, because it undergoes cycles of both reduction and oxidation. When the molecule loses electrons, it becomes oxidized forming GSSG that gains electrons through reduction processes and re-converted into the reduced form (GSH). An increased GSSG/GSH ratio is a highly indicative marker of high levels of oxidative stress. GSH redox status is under the control of a biological mechanism involves both GPx which catalyzes the oxidation of GSH and GR which catalyzes the reduction of GSH, using NADPH as a hydrogen donor (Nishanthi 2014). So, the renal activities of these enzymes (GPx and GR) together with the level of GSH are used as a marker for oxidative stress and cytotoxicity.

GSH is also very essential for detoxification of certain xenobiotics by conjugation reactions in phase II metabolism. Conjugation reactions for GSH are catalyzed by GST in the cytosol and they represent an important mechanism of eliminating electrophilic xenobiotics in the liver (Meister 1994). The enzyme GST has also been found to exert antioxidant effects particularly in the peroxide-containing compounds, using GSH for reduction process (Ketterer 1990).

It has been reported that, free radicals-induced oxidative damage, particularly ROS as well as NO, have been proposed as common mediators for apoptosis (Ozben 2007 & Iwakiri 2015). The process of apoptosis takes place through either one of two major pathways, the intrinsic mitochondrial or extrinsic death receptor pathway (Kroemer 2007). Induction of p53, Bax and Bak, and inhibition of the anti-apoptotic effect of Bcl-2 and Bcl-xL seems to be implicated in the intrinsic mitochondrial pathway of apoptosis. This pathway results in marked disruption of mitochondrial membrane permeability and subsequent release of apoptogenic proteins, such as cytochrome c, which lead to caspases activation and ultimately apoptosis.

In the extrinsic death receptors pathway, the receptors located at the cellular membrane, which include Fas receptors, tumor necrosis factor (TNF) receptors, and TNF-related apoptosis-inducing ligand receptors, recruit adaptor proteins including initiator caspase-8, which trigger the activation of effector caspases (-3, -6, -7) leading finally to cell apoptosis (Ketterer 1990).

In the current study, administration of CA in rats was found to induce apoptosis. Obtained results exhibited dose-dependent marked increases in the renal content of the pro-apoptotic markers, p53 and caspase-3 while the anti-apoptotic Bcl-2 was decreased. In this regard, several published *in vitro* studies on the cytotoxic effect of CA on human cancer cell lines have been reported (Ohara 2004).

In recent years, a significant interest could be observed regarding the exploration of an alternative or complementary chemotherapeutic drugs of plants origin for diseases treatment or protection against adverse side effects induced by synthetic drugs. Cin which belongs to Cinnamomum genus possesses strong aromatic and medicinal properties (Eidi 2012). Cin is a potent antioxidant and it is safely used in the medicinal purposes with non-remarkable adverse side effects16.

Interestingly, the present study addressed, for the first time, the potential protective impact of Cin extract against CA-induced kidney injury, oxidative stress and apoptosis in albino rats. Obtained results demonstrated that, treatment with Cin decreased serum concentration of Cr, Ur and UA, as compared to CA-treated groups, suggesting the ability of Cin to protect against CA-induced renal injury. Furthermore, by Cin the redox status of the kidney was greatly improved, and the oxidative stress was suppressed as reflected by significantly decreased renal MDA, PC, H_2O_2 and NO; and markedly increased antioxidants (GSH, SOD, CAT, GPx, GR and GST) when compared to groups treated with AC alone.

In this line, Cin extract was found to improve renal injury induced by cypermethrin as indicated by decreased serum concentration of Cr, Ur and UA (Sakr 2014). Also, the ability of Cin to diminish oxidative stress through reducing LPO and increasing the activity of the antioxidant enzymes has been reported (Lobo 2010). Similarly, in CCl_4-treated rats, prior administration of Cin extracts attenuated toxin-induced adverse effects on renal levels of SOD, GPx and GSH (Moselhy 2009).

In the current study, the protective impact of Cin extract against CA- induced apoptosis in rats was also evaluated. The results obtained showed significant decreases in the renal contents of the pro-apoptotic markers; p53 and caspase-3 accompanied with significant elevation in Bcl-2; the anti-apoptotic marker, in rats treated with CA and Cin, when compared to groups treated with CA alone. This result suggested that Cin extract might be beneficial in the protection against CA-induced apoptosis in the kidney of rats (Nicolai 2015).

6. CONCLUSION

-The obtained results provided additional evidence that treatment with CA in male rats may have potential nephron-toxicity mainly through triggering oxidative stress and apoptosis.

-Administration of Cin extract along with CA may cause considerable protective effect against CA-induced h renal oxidative tissue damage and apoptosis in albino rats.

-This nephroprotective e effect of cinnamon could be attributed largely to its antioxidant activity and its ability to scavenge free radicals.

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