

Evaluating the Protective Impact of Ginger Extract Against Ciprofloxacin-Induced Hepatotoxicity in Male Albino rats

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Abstract: In the present study, potential protective impact of ginger extract against ciprofloxacin (CPFX)-induced hepatotoxicity in male rats was investigated. Forty-two adult male albino rats were divided into seven groups: control, dimethyl sulphoxide (DMSO), ginger (200 mg/kg), CPFX₂₀ (20 mg/kg), CPFX₂₀ plus ginger, CPFX₄₀ (40 mg/kg) and CPFX₄₀ plus ginger. Both CPFX and ginger doses were orally given to rats for 10 consecutive days. At the end of the experiment, serum and liver samples were processed for biochemical assays. Obtained results exhibited that treatment of rats with CPFX produced marked increases in serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and total bilirubin. Also, CPFX markedly increased hepatic contents of malondialdehyde (MDA), protein carbonyl (PC), hydrogen peroxide (H₂O₂) and nitric oxide (NO). In addition, the drug induced depletion in the hepatic levels of antioxidant parameters including reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GRd) and glutathione-s-transferase (GST). CPFX was also found to induce apoptosis in the hepatic cells as indicated by increased level of p53 and caspase-3 accompanied with decreased level of Bcl-2. The deleterious effects of CPFX on all measured biochemical indices seemed to be dose-dependent. Concurrent treatment with ginger extract and CPFX in rats significantly mitigated the CPFX-induced oxidative stress and apoptosis, and greatly recovered the biomarkers of the hepatocellular injury. This study addressed, for the first time, that ginger extract may be useful in the protection against liver damage induced by CPFX. The hepatoprotective impact of ginger might be mediated primarily by its potent antioxidant activity and its ability to scavenge free radicals.

Key words: ciprofloxacin, ginger, liver, aminotransferase, oxidative stress, apoptosis

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I. Introduction

CPFX is a fluorinated quinolone antibiotic that frequently used to treat many of bacterial infectious diseases, such as infection of the urinary tract, lower respiratory tract and skin. However, potential hepatotoxicity has been reported in patients treated with therapeutic doses of CPFX.¹ Published data on human patients showed that the drug can cause acute liver injury, which is associated with markedly elevated activity of serum transaminases. CPFX can also induce cholestatic pattern of liver injury which usually occurs after a long-time treatment with the antibiotic.² In experimental animals, CPFX was found to induce marked increase in the serum activities of liver injury markers ALT, AST and ALP.³

Cumulative evidence both *in vivo* and *in vitro* showed that generation of reactive oxygen species and oxidative stress were implicated in the mechanism of CPFX-induced cytotoxicity. It has been reported that administration of CPFX in mice induced lipid hydroperoxide in the liver.⁴ Also, in pregnant rats, CPFX caused elevation in the levels of MDA and inhibition in the activity of GPx, SOD and CAT in the liver of fetuses obtained on day 21 of gestation.⁵ On the other hand, CPFX can cause apoptosis in different types of tumor cell lines.^{5,6} *In vivo* studies, long-term administration of CPFX significantly increased the apoptotic germ cells in testis of the rats.⁷

Ginger (*Zingiber officinale*) is commonly used as food spice all over the world. In addition, the herb extract has been traditionally used for the treatment of various types of diseases such as rheumatism, diabetes, asthma, stroke, gingivitis, catarrh, nervous diseases, toothache and constipation.⁸ The therapeutic efficacy of ginger extract is attributed, in part, to the presence of polyphenol compounds (6-gingerol and shogaols) which exhibit antioxidant, anti-inflammatory and anti-tumor properties.⁹ Several studies showed that ginger extracts can be used in the protection against various xenobiotics-induced toxicity. Of published data, ginger extracts was found to protect against cisplatin-induced liver injury,¹⁰ bromobenzene-induced hepatic damage¹¹ and CCl₄-induced hepatotoxicity.¹² Based upon the above information, the present study was conducted to evaluate, for the first time, the potential protective impact of ginger extract against CPFX-induced adverse changes in the biochemical markers of liver injury, oxidative stress and apoptosis in male Wistar albino rats.

II. Materials and methods

1. Animals

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

2. Drug and doses preparation

CPF_X (750 mg) was purchased from local pharmacy at Mansoura city, Egypt in the form of film coated tablets. The tablets were grind until it became powder, then suspended in distilled water (w/v). Drug suspension then was given daily to the rats according to the selected doses (20 and 40mg/kg).

3. Preparation of the ginger extract

Fresh ginger rhizomes were purchased from local aromatherapy market at Mansoura city, Egypt. The ginger rhizomes were washed well, dried and about 100 g was grinded to form powder. The ginger powder was mixed with 2 liters of 70% ethanol in bottle for 72 hours. The suspension was filtered and the filtrate, which contains the active components of ginger, was collected and let stand at room temperature for 5 days to evaporate ethanol.¹³ After complete evaporation of ethanol, a semi-solid extract (viscous oily mass) was produced, weighed and dissolved in DMSO (10%). Each rat, according to its weight, received orally a volume from the ginger solution which contains amount of ginger equivalent to the selected dose concentration (200 mg/kg).

4. Experimental design

After two weeks of acclimatization, rats were allocated randomly into seven groups, six rats per each, as follows:

- i. Control group: received no chemical treatment.
- ii. DMSO group: received diluted DMSO (10%).
- iii. Ginger-treated group: received ginger extract in a dose of 200 mg/kg.¹⁴
- iv. CPF_{X20mg}-treated group: received CPF_X in a dose of 20 mg/kg.¹⁵
- v. Ginger plus CPF_{X20mg}-treated group: received ginger extract (200 mg/kg) and CPF_X (20 mg/kg).
- vi. CPF_{X40mg}-treated group: received CPF_X in a dose of 40 mg/kg.¹⁵
- vii. Ginger plus CPF_{X40mg}-treated group: received ginger extract (200 mg/kg) and CPF_X (40 mg/kg).

All used chemicals were given by gavage once a day for 10 consecutive days. At the end of the experiment, overnight fasted rats were anesthetized with intraperitoneal injection of a dose of 10ml/kg of ketamine/xylazine. Then, blood was collected by cardiac puncture using a vacuum tube and centrifuged at 3000 rpm for 20 min. Serum was carefully separated and each sample was labeled and kept at -20 °C until biochemical analysis. Tissue samples were obtained from the right lobe, cleaned, weighed and stored at -20°C for biochemical analysis. For practical use, liver samples were removed from the deep freezer, homogenized in phosphate-buffered saline to form 10% (w/v), and the homogenates were centrifuged at 1000 rpm for 5 min to separate the supernatant.

Biochemical assay

Serum levels of ALT, AST, ALP, GGT and total bilirubin were determined according to the methods described in Murray,¹⁶ Wenger *et al.*,¹⁷ Gendler¹⁸ and Levitt and Levitt¹⁹ respectively. The level of hepatic MDA was assayed by the method of Ohkawa *et al.*²⁰ Liver content of PC was evaluated as described by Dalle-Donne *et al.*²¹ The concentration of H₂O₂ in liver tissue was measured by the procedure of Aebi.²² The level of hepatic NO was evaluated by the procedure of Montgomery and Dymock.²³ Liver content of GSH was assayed according to the method of Beutler.²⁴ Hepatic activity of antioxidant enzymes SOD, CAT, GPx, GRd and GST were estimated on the basis of the procedures of Aebi,²² Paglia and Valentine,²⁵ Nishikimi *et al.*,²⁶ Habig²⁷ and Goldberg and Spooner²⁸ respectively. For the flow cytometric analysis of p53, caspase-3 and Bcl-2; samples from the liver homogenates were prepared according to the method described by Gong *et al.*²⁹

Statistical analysis

Results obtained were analyzed using one-way analysis of variance (ANOVA) test followed by Duncan's multiple range tests. The data were expressed as a means ± SE and $P \leq 0.05$ was considered to be statistically significant.

III. Results

Obtained results in table (1) show significant increases in the serum levels of ALT, AST, ALP, GGT and total bilirubin, in a dose-dependent manner, after oral treatment with CPF (20 mg/kg and 40 mg/kg) in rats, in comparison with control group. However, concurrent treatment with CPF and ginger extract displayed significant decreases in the serum levels of mentioned diagnostic markers of liver injury, as compared to groups treated with CPF alone.

Table 2 exhibits that administration of CPF alone in rats produced dose-dependent significantly increased hepatic content of oxidative stress markers including MDA, PC, H₂O₂, NO, when compared to control group. On contrary, CPF produced marked decreases in the hepatic levels of antioxidants GSH, SOD, CAT, GPx, GR and GST, in association with the applied dose, when compared to control results. Treatment with ginger extract in rats treated with CPF significantly attenuated the elevated hepatic contents of oxidative stress markers and increased the lowered levels of antioxidant parameters in the liver, as compared to groups treated with CPF alone.

In table (3) and figures (1, 2 and 3), obtained results displayed that administration of CPF in rats caused dose-dependent changes in apoptotic markers in the liver. The results showed marked increase in the hepatic levels of p53 and caspase-3 parallel to significant decrease in the level of Bcl-2. Co-administration of ginger with CPF attenuated the apoptotic activity of CPF, as the results displayed significant decreases in both p53 and caspase-3 accompanied with significant increase in the level of Bcl-2, in comparison with groups treated with CPF alone.

Treatment of rats with either ginger or DMSO has no adverse effect on any of the investigated biochemical parameters (Tables 1, 2 and 3).

Table 1: Effect of ginger extract on CPF-induced changes in the markers of liver status in serum of male rats.

	Con	DMSO	Ging	CPF 20	Ging + CPF 20	CPF 40	Ging + CPF 40
ALT(u/l)	26.17± 2.06	26.65± 1.91	25.71± 2.03	72.41± 1.42 ^a	33.64± 2.21 ^{ab}	91.63± 2.95 ^a	38.57± 2.01 ^{ac}
AST(u/l)	88.11± 2.86	88.25± 2.68	87.70± 1.80	148.0± 3.15 ^a	103.3± 2.90 ^{ab}	166.2± 3.78 ^a	114.6± 4.86 ^{ac}
ALP(u/l)	60.07± 3.10	59.91± 3.03	59.67± 2.71	97.60± 2.89 ^a	71.84± 2.18 ^{ab}	124.7± 2.50 ^a	81.61± 3.61 ^{ac}
GGT(u/l)	7.52± 0.36	7.51± 0.36	7.42± 0.37	20.18± 0.96 ^a	9.62± 0.71 ^{ab}	31.63± 1.49 ^a	11.74± 0.90 ^{ac}
TB(mg/dl)	0.109±0.005	0.109± 0.004	0.109± 0.005	0.414± 0.012 ^a	0.132±0.005 ^{ab}	0.511± 0.007 ^a	0.137±0.003 ^{ac}

- Con = Control, Ging = Ginger
- Values were expressed as mean ± SE (n = 6 for each groups).
- a, b and c = significantly difference at $p \leq 0.05$ comparing to control, CPF 20 mg and CPF 40mg groups respectively.

Table 2: Effect of ginger extract on CPF-induced oxidative stress in the liver of male rats.

	Con	DMSO	Ging	CPF20	Ging + CPF20	CPF40	Ging + CPF 40
MDA (nmol/g)	9.39± 0.31	9.13± 0.49	9.08± 0.38	28.30± 1.37 ^a	11.81± 0.74 ^{ab}	39.11± 1.29 ^a	14.29± 1.11 ^{ac}
PC(nmol/g)	12.97± 0.63	12.15± 0.780	12.04± 1.02	38.77± 1.32 ^a	17.17± 0.83 ^{ab}	50.11± 1.27 ^a	20.47± 1.61 ^{ac}
H ₂ O ₂ (mM/g)	119.5± 3.47	117.7± 2.67	116.8± 4.72	166.6± 2.54 ^a	132.9± 2.61 ^{ab}	185.1± 4.25 ^a	137.8± 3.21 ^{ac}
NO (µmol/g)	38.65± 1.81	38.62± 2.02	38.44± 1.54	78.47± 1.43 ^a	51.38± 2.70 ^{ab}	92.99± 1.48 ^a	55.95± 2.74 ^{ac}
GSH (mg/g)	4.86± 0.20	4.76± 0.15	4.90± 0.16	1.55± 0.15 ^a	3.66± 0.24 ^{ab}	0.83± 0.05 ^a	3.450± 0.15 ^{ac}
SOD (u/g)	118.9± 3.03	118.2± 2.37	119.7± 2.14	66.54± 1.95 ^a	101.0± 2.55 ^{ab}	53.09± 1.62 ^a	94.35± 3.27 ^{ac}
CAT(u/g)	146.7± 2.20	147.1± 2.12	148.3± 2.83	84.22± 3.88 ^a	137.1± 2.90 ^{ab}	72.60± 2.39 ^a	127.8± 2.53 ^{ac}
GPx(u/g)	6.52± 0.17	6.52± 0.25	6.63± 0.17	2.09± 0.09 ^a	5.38± 0.21 ^{ab}	1.84± 0.07 ^a	5.15± 0.21 ^{ac}
GRd (u/g)	9.59± 0.30	9.57± 0.51	9.70± 0.46	4.16± 0.17 ^a	7.88± 0.23 ^{ab}	2.92± 0.13 ^a	7.13± 0.32 ^{ac}
GST (u/g)	24.74± 1.50	24.75± 0.91	25.54± 1.34	12.24± 0.92 ^a	20.11± 0.65 ^{ab}	7.265± 0.49 ^a	18.22± 0.41 ^{ac}

- Con = Control, Ging = Ginger
- Values were expressed as mean ± SE (n = 6 for each groups).
- a, b and c = significantly difference at $p \leq 0.05$ comparing to control, CPF 20 mg and CPF 40mg groups respectively.

Table 3: Effect of ginger extract on CPF-induced apoptosis in the liver of male rats.

	Con	DMSO	Ging	CPF 20	Ging + CPF 20	CPF 40	Ging + CPF 40
p53 (%)	26.43± 1.08	27.07± 0.84	26.23± 1.34	58.20± 1.81 ^a	35.37± 2.05 ^{ab}	68.47± 2.03 ^a	46.47± 1.67 ^{ac}
Caspae-3 (%)	21.67± 2.36	21.53± 1.73	20.80± 1.67	56.37± 1.44 ^a	33.47± 1.34 ^{ab}	68.93± 1.29 ^a	42.70± 1.30 ^{ac}
Bcl-2 (%)	58.20± 0.96	56.30± 0.69	57.73± 1.05	28.27± 0.75 ^a	46.83± 1.06 ^{ab}	23.00± 1.51 ^a	38.57± 1.38 ^{ac}

- Con = Control, Ging = Ginger.
- Values were expressed as mean ± SE (n = 6 for each groups).
- a, b and c = significantly difference at $p \leq 0.05$ comparing to control, CPF 20 mg and CPF 40mg groups respectively.

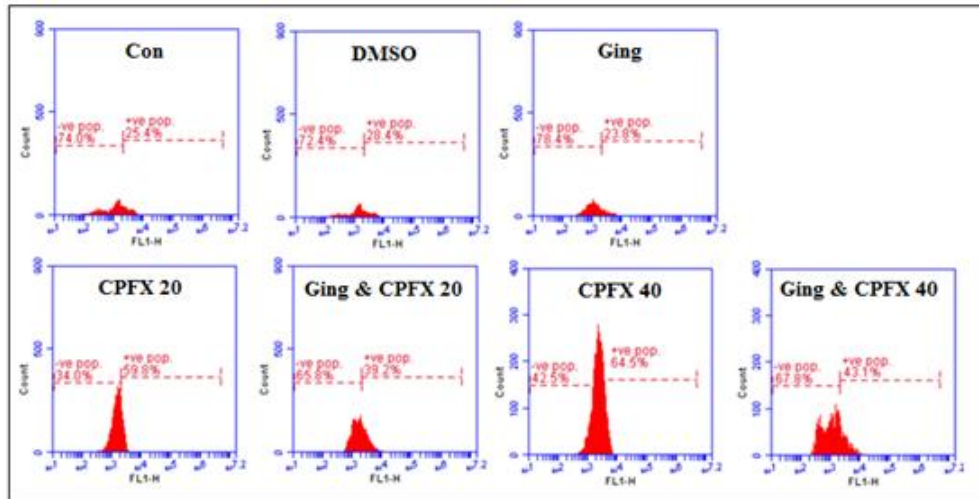


Figure 1: Flow cytometry chart showing data generated by BD Accuri™ C6 for determination of p53 in the liver of different animal groups. Con = Control, Ging = Ginger.

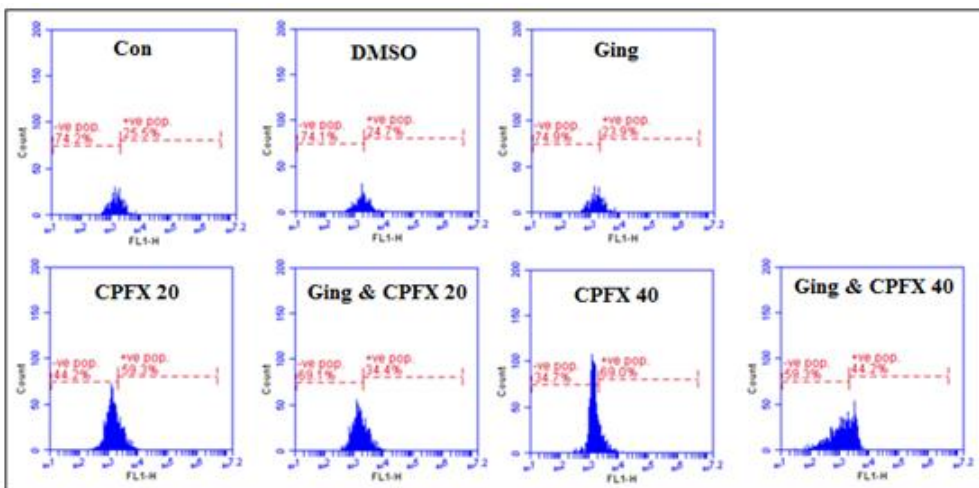


Figure 2: Flow cytometry chart showing data generated by BD Accuri™ C6 for determination of caspase-3 in the liver of different animal groups. Con = Control, Ging = Ginger.

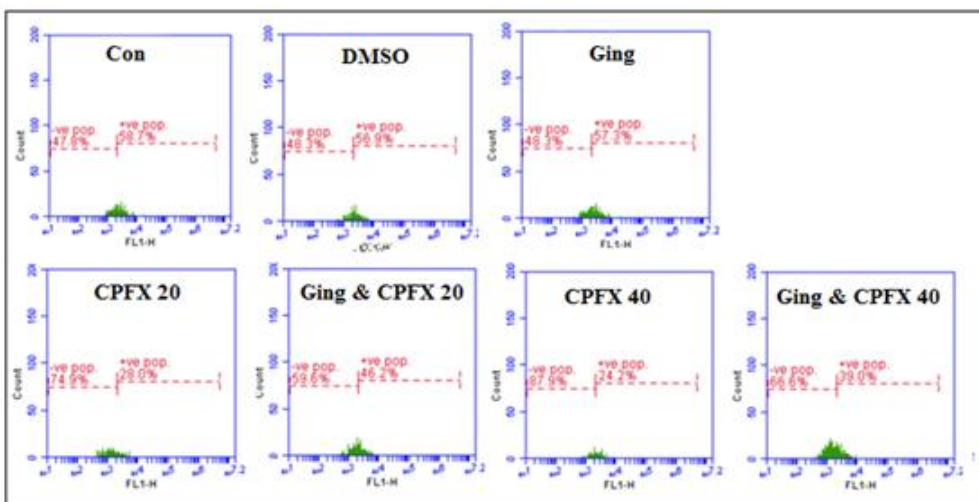


Figure 3: Flow cytometry chart showing data generated by BD Accuri™ C6 for determination of Bcl-2 in the liver of different animal groups. Con = Control, Ging = Ginger.

IV. Discussion

Potential hepatotoxicity may be associated with the treatment with CPFY in both human and animals, because the drug is mainly metabolized in the liver.¹ In the present study, administration of CPFY to rats was found to produce dose-dependent significant elevation in the levels of serum transaminases (ALT and AST), ALP, GGT and total bilirubin. This finding provided evidence that CPFY may cause hepatocellular injury and hepatobiliary disorder in rats. In this line, several clinical reports demonstrated liver injury in most patients administered CPFY which was characterized by elevation in serum level of bilirubin and activity of liver enzymes ALT, AST, ALP and GGT.¹ In animal studies, treatment of rabbits with CPFY was also found to produce significant increase in serum activities of AST, ALT and ALP.³

Although the mechanisms by which CPFY induced hepatocyte injury are not fully understood, implication of oxidative stress has been suggested. It has been reported that, development of CPFY-induced liver injury may be resulted from the production of free radicals which initiate the process of lipid peroxidation and oxidative stress. This may lead to destroy the membranes of hepatocytes leading to the release of their cytosolic enzymes into the blood.¹ Present results confirmed this statement and added support that CPFY can cause oxidative stress and liver injury in the treated rats. The results showed dose-dependent significant increases in the hepatic content of MDA, PC, H₂O₂ and NO following treatment of rats with CPFY. Of previous studies, Weyers *et al.*⁴ found that treatment of mice with a single dose of CPFY (100mg/kg) produced lipid peroxidation in the liver tissue after 15-60 minutes of drug administration, as indicated by increased level of hepatic lipid hydroperoxide (LOOH). Also, Taslidere *et al.*³⁰ recorded increases in the liver contents of MDA in rats treated with CPFY. Beside induction of lipid peroxidation, CPFY-increased hepatic content of PC (the marker of protein oxidation) in the present study raised the possibility that CPFY has the potential to induce oxidative stress and tissue damage. Published data showed that treatment with CPFY in rats was found to produce protein and lipid oxidation, as indicated by increased hepatic advanced oxidized protein products and MDA levels.³¹

Overproduction of the free radical NO is toxic to the cell, thus increased hepatic content of this reactive molecule may represent a part of mechanism of CPFY-induced hepatotoxicity. In this regard, previous studies exhibited oxidative stress which accompanied with significant elevation in NO content in brain of mice and kidney of rats following treatment with CPFY.^{32,33} It has been reported 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.³⁴ Based on the ability of CPFY to stimulate the production of free radicals NO and O₂⁻, production of ONOO⁻ during treatment with CPFY might be occurred, and implication of it in the mechanisms of CPFY-induced oxidative tissue damage in the liver is not excluded.

Induction of oxidative tissue injury by CPFY in the current study could reflect disturbance of cellular antioxidant system that detoxifies free radicals and reactive oxygen species. In this context, present finding demonstrated dose-dependent marked decreases in the level of GSH and activity of antioxidant enzymes including SOD, CAT, GPx, GRd and GST in the liver of rats treated with CPFY. This result together with increased oxidant products (MDA and PC) and reactive molecules NO indicated that CPFY induced oxidative stress in the treated rats. In previous studies, CPFY decreased the level of GSH and activity of GPx parallel to production of lipid peroxidation and histopathological alterations in the liver of treated rats, suggesting oxidative stress and liver damage.³⁰

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. GSH redox status is under the control of a biological mechanism involves both GPx which catalyzes the oxidation of GSH and GRd which catalyzes the reduction of oxidized form of GSH, using NADPH as a hydrogen donor.³⁵ So, the hepatic activities of these enzymes (GPx and GRd) together with the level of GSH are used as markers for oxidative stress and cytotoxicity. GSH is also very essential for detoxification of certain xenobiotics by conjugation reactions in phase II metabolism. Conjugation reactions of GSH are catalyzed by GST in the cytosol and they represent an important mechanism of eliminating electrophilic xenobiotics in the liver. The enzyme GST has also been found to exert antioxidant effects particularly in the peroxide-containing compounds, using GSH for reduction process.³⁶ In this regard, it could be suggested that, the reduction in the GSH and its associated enzymes, GPx, GRd and GST, in the liver tissue of rats treated with CPFY in the present study might represent a part of the mechanisms of CPFY-induced hepatotoxicity.

The term apoptosis is applied to the death of cell under controlled cellular program that occurs in multicellular organisms under normal and abnormal physiological condition. The process of apoptosis takes place through either one of two major pathways, the intrinsic mitochondrial or extrinsic death receptor pathway.³⁷ Induction of apoptotic effect 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.³⁷

In the current study, administration of CPFEX in rats was found to induce apoptosis. Obtained results exhibited dose-dependent marked increases in the hepatic content of the apoptotic markers, p53 and caspase-3 in CPFEX-treated rats. Meanwhile, the anti-apoptotic Bcl-2 in the liver was significantly decreased following exposure to CPFEX in rats. In this regard, several published *in vitro* studies on the cytotoxic effect of CPFEX on human cancer cell lines showed the apoptotic activity of CPFEX. Of these studies, Aranha *et al.*⁶ recorded cell cycle arrest at the S/G2-M, up-regulation of Bax, altered the Bax/Bcl-2 ratio and induction of apoptosis in the CPFEX-treated bladder tumor cells line. In the animal studies, administration of CPFEX in rats was found to produce oxidative stress accompanied with histopathological alterations which included apoptotic bodies.³⁰ In addition, long-term administration of CPFEX in rats led to induction of apoptosis in the germ cells of seminiferous tubules.⁷ However, CPFEX-induced apoptosis in the liver could be attributed to its ability to produce free radicals and oxidative stress.

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. Ginger (*Zingiber officinale*) which belongs to Zingiberaceae family possesses strong aromatic and medicinal properties. The herb contains a potent antioxidant compounds and it is safely used in the medicinal purposes with non-remarkable adverse side effects.^{9,11} Moreover, ginger can be used in the treatment of various bacterial infections, as it has a direct anti-microbial activity.³⁸ In the present study, we investigated the potential protective effect of ginger extract against the CPFEX-induced liver injury, oxidative stress and apoptosis in albino rats.

Obtained results showed that, treatment with ginger mitigated CPFEX-induced liver injury and hepatobiliary disorder. This was indicated by observed significant decrease in the levels of liver diagnostic markers including ALT, AST, ALP, GGT and total bilirubin in the serum of rats treated with ginger extract along with CPFEX, as compared to groups treated with CPFEX alone. Furthermore, the redox status of the liver was greatly improved and the oxidative stress was suppressed following combined treatment with ginger extract and CPFEX, as reflected by significantly decreased hepatic content of MDA, PC, H₂O₂ and NO; and markedly increased the activity of hepatic antioxidants including GSH, SOD, CAT, GPx, GRd and GST, when compared to rats treated with CPFEX alone. These results could suggest that ginger has a hepatoprotective impact against CPFEX-induced oxidative stress. Present findings are consistent with previous studies which reported the ability of ginger extract to modulate beneficially the adverse changes in the markers of hepatocellular injury including activities of ALT, AST, ALP; and levels of total bilirubin in the serum of rats treated with various xenobiotics like CCl₄ and Adriamycin.^{12,39}

The ability of ginger extract to reduce CPFEX-induced hepatic cells injury could be attributed to its antioxidant activity which protects the hepatocytes membranes against lipid peroxidation leading to maintenance of stabilization of membranes and finally prevention of leakage of liver enzymes. The present finding together with previously published data demonstrated the ability of ginger to diminish oxidative tissue damage through reducing lipid peroxidation and increasing the activity of the antioxidant enzymes. In rats intoxicated with bromobenzene, pretreatment with ginger extract attenuated toxin-induced adverse effects, as the herb extract increased the hepatic levels of SOD, GPx and GSH.¹¹ Ginger extract was also found to mitigate adriamycin-induced oxidative tissue damage in the liver through decreasing the level of MDA and elevating the activity of SOD.⁴⁰ Similarly, ginger beneficially modified the undesirable changes in the plasma and hepatic levels of some oxidative stress parameters including GSH, SOD and CAT in rats intoxicated by lead.⁴¹ In recent studies, ginger extract exerted protective effects against production of lipid peroxidation and reduction in the levels of antioxidant enzymes in the liver of rats treated with CCl₄¹² and metalaxyl.⁴² It is noteworthy that, the hepatoprotective impact of ginger is thought to be mediated, at least in part, by modulating the redox status in the liver. Previous studies demonstrated the ability of the antioxidant compounds of ginger to scavenge the free radicals such as O₂⁻, ·OH and NO,⁴³ which is mainly generated after exposure to CPFEX.³³ Ginger has also been reported to suppress the pro-inflammatory mediator NO production by partially inhibiting enzymatic activity of inducible NO synthase.⁴⁴

In the current study, the protective impact of ginger extract against CPFEX-induced apoptosis in rats was also evaluated. Obtained results showed significant decreases in the hepatic contents of apoptotic markers p53 and caspase-3 accompanied with significant elevation in the anti-apoptotic marker Bcl-2 in rats treated with CPFEX and ginger, when compared to groups treated with CPFEX alone. This results suggested the ability of ginger extract to protect the liver of rats against CPFEX-induced apoptosis. Present finding is consistent with several previous studies which demonstrated the anti-apoptotic activity of ginger. Khaki and Khaki⁴¹ reported that ginger markedly suppressed lead acetate-induced apoptosis in the liver of rats. Also, ginger extract was

found to reduce the percent of apoptotic cells and the number of Bax-positive cells in testis of mice treated with metiram³⁹. Additionally, *in vitro* study, pretreatment with ginger extract remarkably reduced the IL-1 β -induced elevation in apoptotic markers, Bax/Bcl-2 ratio and caspase-3 activity in C28I2 human chondrocytes.⁴⁵ In recent study, administration of ginger induced an anti-apoptotic effect as indicated by suppressed metalaxyl-induced increase in the Bax, caspases-8 gene expression and DNA damage in the liver tissue of rats.⁴²

V. Conclusion

1. Present finding of rats administered CPFY added support that treatment with CPFY may induce hepatotoxicity. So, in human therapy with CPFY, it is recommended to monitor the markers of liver injury in the blood serum.
2. Treatment with ginger extract together with CPFY produced significant protective impact against CPFY-induced liver injury, oxidative stress and apoptosis in albino rats. This hepatoprotective effect of ginger might be mediated primarily by its antioxidant activity, as well as its ability to scavenge free radicals.

Declaration of interest:

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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