Hepatoprotective Activity of Curcumin against Rifampicin-Induced Genotoxicity in Experimental Mice

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Abstract: Tuberculosis is a dangerous disease and its death toll is increasing year by year. Intake of rifampicin, the most common antitubercular drug, leads to fatal genotoxic effects on hepatocytes. We have studied the protective effect of curcumin supplementation against the genotoxic effects induced by administration of rifampicin (80mg/kg B.wt.) for four weeks orally in male mice. Curcumin(175mg/kg B.wt.) were administered orally 2 hours prior to rifampicin administration. We showed that the serum level of 8-hydroxy- 2'-deoxyguanosine (8-OHdG), A marker widely used for oxidative damage to DNA were significantly increased in mice treated with rifampicin also there was an elevation in the level of gene expression of 8-oxoguanine DNA-glycosylase 1(OGG1). administration of rifampicin caused an increase in DNA damage in liver of male mice indicated by the damaged nuclei (comet tail length and % of DNA damage). In addition, The liver tissue of male mice treated with rifampicin showed a decrease in the level of gene expression of anti oxidant enzymes (glutathion -s transferase α2, glutathion -s-transferase μ2 and catalase ).The co-treatment with curcumin significantly attenuated rifampicin induced gene toxicity in hepatocytes indicated by the significant decrease in the serum level of 8-OHdG, decrease in damaged nuclei explained by comet assay (tail length and % of DNA damage), also Levels of gene expression of anti oxidant enzymes were also maintained to near normal level by curcumin co-administration. From the results obtained, it can be concluded that curcumin is beneficial against rifampicin-induced hepatic genotoxicity, also can used as a prophylactic measures.


http://www.jofamericanscience.org, 39

Keywords: Rifampicin, genotoxicity, curcumin, 8-OHdG, comet assay

1. Introduction

Genotoxicity is the genetic damage, due to DNA damaging agents including drugs by different mechanisms. The induction of genetic damage is a critical step in the production of different genetic diseases in future generations, birth defects and contributes to somatic diseases such as cancer in the present generation. Therefore it is necessary to evaluate the genotoxic potential of drugs to evaluate their ability to cause cancer and other defects. Genotoxic potential of drugs is assessed, as part of the safety evaluation process and genotoxicity assays have become an integral component of drug regulatory requirements (Jena et al., 2002).

Rifampicin, an antibacterial drug, is highly effective in the treatment of tuberculosis and leprosy. Recently, it has been reported to have neuroprotective effects in vitro and in vivo models.(Oida et al.,2006). Rifampicin (RIF) is a semisynthetic derivative of the complex macrocyclic antibiotic rifamycin obtained from a streptomycyes organism. It is the first antibiotic of the ansamycin family. The antimicrobial activity of RIF is due to its inhibition of bacterial RNA polymerase (RNAP). RIF binds to conserved amino acids in the active centre of the enzyme and blocks transcription initiation. (Audrey et al., 2010).

Rifampicin, being the first line drug used as antituberculous chemotherapy, is known to be associated with hepatotoxicity. (Tasduq et al., 2005). The rate of hepatic damage has been reported to be much higher in developing countries (8- 30%). Oxidative stress produced by RIF causes hepatic injury, (Sodhi et al., 1997). Majority of normally formed free radicals are removed by the action of reduced glutathione. This causes the initiation of lipid peroxidation (LPO) resulting in tissue injury (Shanker et al., 2005). Reactive oxygen species play an important role in rifampicin induced liver injury (Chowdhury et al., 2006).

The oxidation of DNA bases is produced by reactive oxygen species (ROS), as well as other processes leading to increased oxidation. ROS are generated both from endogenous sources and from the reactions of xenobiotics. The agents producing DNA oxidation in vivo are generally believed to do so as a result of increased production of ROS. (Kasai, 1997).

ROS plays an important role in mediating cellular responses , 8-OHdG is a byproduct of ROS damage to DNA, which can cause mutation of G:C to A:T if it remains in the DNA at the time of replication , 8-OHdG in urine and blood is a widely accepted marker of oxidative DNA damage and oxidative stress. Normal DNA repair removes 8-OHdG adducts,
which are excreted and measurable in urine, blood and tissues. (Breton et al., 2007).

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, 1) is a naturally occurring phenolic compound isolated as a yellow pigment from turmeric (dry rhizomes of Curcumin longa) which is commonly used as a spice and food colorant (Buescher and Yang, 2000). This compound has been reported to possess a variety of biological and pharmacological activities, including anti-oxidative (Daniel et al., 2004), anti-inflammatory (Chainani-Wu, 2003), anticarcinogenic (Aqarwal et al., 2003) and anti-HIV (Mazumder et al., 1995).

The antioxidant mechanisms of curcumin have recently been the focus of interest of free-radical chemists and biologists. Curcumin is known to protect biomembranes against peroxidative damage. Peroxidation of lipids is known to be a free-radical-mediated chain reaction, leading to the damage of the cell membranes, and the inhibition of peroxidation by curcumin is mainly attributed to the scavenging of the reactive free radicals involved in the peroxidation. Most of the antioxidants have either a phenolic functional group or a β-diketone group. Curcumin is an unique antioxidant, which contains a variety of functional groups, including the β-diketo group, carbon–carbon double bonds, and phenyl rings containing varying amounts of hydroxyl and methoxy substituents (Wright, 2002).

2. Material and methods:

I- Experimental animals:
A total 40 Male white Swiss mice aged 9–12 weeks will be used in all experiments. The animals will be obtained from central animal house of Veterinary Medicine, Zagazig University. Animals housed in stainless steel cages, maintained under hygienic conditions and received standard diet and water two weeks before starting the experiment to accommodate them to the experimental condition in the laboratory.

II- Tested compounds
Ciprofloxacin (CPX): purchased from Amoun Pharmaceutical Co., Egypt. used by a dose (130mg/kg B.Wt/day).

Rifampicin: is produced by Novartis Pharma, Cairo. used by a dose (80mg/kg B.Wt/day).

Curcumin: It was obtained in commercial form (Turmeric Extract with BioPerine® Directions). The drug was obtained from Vitacost, USA. used by a dose (175mg/kg B.wt/day). Piperine is an adjuvant used to improve the bioavailability of curcumin by interferes with glucuronidation.

III- Animal grouping
The rout of administration of all treatments are orally by using stomach tube. The experimental animals were randomly divided into 4 groups 10 of each as following:

Group A: (N=10), control group received normal saline.

Group B: (N=10), received 80mg/kg B.wt. rifampicin for 4 weeks.

Group C: (N=10), received curcumin (175mg/kg B.wt.) then after 2 hours give rifampicin (80mg/kg B.wt.) for 4 weeks simultaneously.

Group D: (N=10), received firstly curcumin (175mg/kg B.wt.) for 1 week then co-treated with curcumin (175mg/kg B.wt.) + rifampicin (80mg/kg B.wt.) for 4 weeks simultaneously.

Methods:
1) Sampling protocol
- Animals will sacrificed using highly sterilized scissors (180°C for 6 hours) to avoid RNA degradation by RNases and latex gloves wearied to minimize RNase contamination.
- Liver samples will immediately excised, part of it will wrapped in aluminium foil and put immediately in liquid nitrogen container to make snap-freezing of tissue and minimize action of endogenous RNase. this part for RT-PCR.
- Another part of liver samples will placed in 1 mL cold HBSS containing 20 mM EDTA/10% DMSO. Mince into fine pieces, let settle, remove and mix 5 - 10 μl with 75 μl LMPA. For comet assay
- Serum samples: blood samples were collected without anticoagulant into clean and dry test tubes for obtaining serum samples which were preserved at –20°C for detection of 8-hydroxy-2’-deoxyguanosine (8-OHdG).

2) Estimation of serum 8-hydroxy-2’-deoxyguanosine (8-OHdG) by ELISA kits:
It was estimated according to the method described by Tomoko et al. (2000)

3) Comet assay:
- The single cell gel electrophoresis / comet assay protocol: by (Singh et al., 1988):

4) Molecular determinations:
- Determination of (Glutathione -s-transferase a2, Glutathione -s-transferase mu 2, catalase, Cytochrome P450 2E1, 8-oxoguanine DNA glycosylase 1) gene expression: Using a semi-quantitative RT-PCR according to (Meadus, 2003).

A- RNA extraction: Total RNA was extracted with E.Z.N.A. spin column RNA extraction kit (Qiagen biotech).

B- Synthesis of cDNA: The Synthesis of cDNA was occurred by using (Qiagen long rang) RT-PCR kits (20). Mat. No. 1042845.

C- PCR amplification.
The PCR amplification was performed using Long-Range 2 step RT-PCR kits from Qiagen.

Table (A): The thermal cycler conditions used during RT-PCR

<table>
<thead>
<tr>
<th>Gene</th>
<th>Initial denaturation</th>
<th>Denaturation</th>
<th>Annealing</th>
<th>Extension</th>
<th>Final extension</th>
<th>Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione transferase α2</td>
<td>95/5 min</td>
<td>94/30 sec</td>
<td>57/30 sec</td>
<td>72/1 min</td>
<td>72/7 min</td>
<td>35</td>
</tr>
<tr>
<td>Glutathione transferase mu 2</td>
<td>94/5 min</td>
<td>94/30 sec</td>
<td>60/45 sec</td>
<td>72/1 min</td>
<td>72/7 min</td>
<td>30</td>
</tr>
<tr>
<td>Cytochrome P450 2E1</td>
<td>95/5 min</td>
<td>91/60 sec</td>
<td>48/60 sec</td>
<td>70/1 min</td>
<td>72/10 min</td>
<td>29</td>
</tr>
<tr>
<td>Catalase</td>
<td>95/5 min</td>
<td>94/30 sec</td>
<td>60/30 sec</td>
<td>72/1 min</td>
<td>72/10 min</td>
<td>35</td>
</tr>
<tr>
<td>8-oxoguanine DNA glycosylase 1</td>
<td>95/5 min</td>
<td>94/30 sec</td>
<td>57/30 sec</td>
<td>72/1 min</td>
<td>72/7 min</td>
<td>35</td>
</tr>
<tr>
<td>GAPDH</td>
<td>95/5 min</td>
<td>94/30 sec</td>
<td>60/30 sec</td>
<td>72/1 min</td>
<td>72/7 min</td>
<td>30</td>
</tr>
</tbody>
</table>

Table (B): Primers used in determination of the expression of the pervious genes. (Yuichi et al., 2007).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Forward primer</th>
<th>Reverse primer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione s-transferase α2</td>
<td>ACATGAAGGAGAGGCTCTGAT</td>
<td>GCAGTCTTGCTCTTTGGT</td>
</tr>
<tr>
<td>Glutathione s-transferase mu 2</td>
<td>TTCCCAATCTGCCCTACTTGA</td>
<td>TCTCCACACAGTTGCTTTC</td>
</tr>
<tr>
<td>Catalase</td>
<td>GCTGAGAGCCCTAAGACGAAT</td>
<td>CTCCTGCCAGCAATGGT</td>
</tr>
<tr>
<td>8-oxoguanine DNA glycosylase 1</td>
<td>GCAACAAGGAAACTGGGAAACT</td>
<td>CAGCATAGGTCCCACAGATT</td>
</tr>
<tr>
<td>Cytochrome P450 2E1</td>
<td>5′ CGGTTCTTGACATCACCCTG3′</td>
<td>5′GCAGGTCACAGGCAATCA3′</td>
</tr>
<tr>
<td>GAPDH</td>
<td>CCCGTAGACAATGGAAGGG</td>
<td>GCCAAGGTGTCATGGATGACC</td>
</tr>
</tbody>
</table>

PCR products were separated on a 1.5% Ethidium bromide treated agarose gel electrophoresis in Tris acetate EDTA buffer with 0.5µg/ml ethidium bromide. The gel examined by UV transilluminator. The electrophoretic picture was taken by digital camera 12 mega pixels and quantified with image J software.

5) Statistical analysis:

The obtained data were analyzed and graphically represented using the statistical package for social science (SPSS, 18.0 software, 2011) for obtaining means and standard error. The data were analyzed using one way ANOVA to determine the statistical significance of differences among groups. Duncan’s test was used for making a multiple comparisons among the groups for testing the inter-grouping homogeneity.

3. Results:

Serum level of 8 hydroxy 2’ deoxy guanosine (8OH2dG)

Table (1): Means ± SE of serum level of 8 hydroxy 2’ deoxy guanosine (8OH2dG) (ng/ml) of the liver tissue of male mice.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group A (Control)</th>
<th>Group B Treated with rifampicin</th>
<th>Group C Treated with rifampicin and curcumin</th>
<th>Group D Treated with curcumin a week prior rifampicin and curcumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Means ± SE</td>
<td>11.075 ± 0.295a</td>
<td>30.20 ± 1.18a</td>
<td>20.56 ± 0.648b</td>
<td>9.925 ± 0.205c</td>
</tr>
</tbody>
</table>

*** Means within the same row carrying different superscripts are very highly significant at (P ≤ 0.001).

Data presented in table (1) show that there was a very high significant increase of serum level of 8 hydroxy 2’ deoxy guanosine (8OH2dG) in group B when compared to the control group, while the level of (8OH2dG) show drastic decrease in( group C) and the decrease in the expression level become nearly around the control group.
Comet assay

Table (4): Means ± SE of Tail length and % of Tail DNA of comet assay of the liver tissue of male mice.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group (Control)</th>
<th>A Group B Treated rifampicin</th>
<th>B Group C Treated rifampicin with curcumin</th>
<th>C Group D Treated with curcumin a week prior rifampicin and curcumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tail length</td>
<td>2.79±0.469c</td>
<td>7.53± 0.241a</td>
<td>4.60 ± 0.296b</td>
<td>5.00 ± 0.246b</td>
</tr>
<tr>
<td>% of Tail DNA</td>
<td>2.70±0.178c</td>
<td>7.25± 0.567a</td>
<td>4.87 ± 0.353b</td>
<td>3.57± 0.290b</td>
</tr>
</tbody>
</table>

*** Means within the same row carrying different superscripts are very highly significant at \( P \leq 0.001 \).

Regarding the oxidative DNA damage caused by rifampicin, the present study was undertaken to test the \textit{in vivo} genotoxic potential of rifampicin in mice using the single cell gel electrophoresis (comet assay). Our result revealed that administration of rifampicin caused an increase in DNA oxidative damage in liver of male mice indicated by the damaged nuclei (comet tail length and % of DNA damage). rifampicin caused very high significant increase in comet tail length and % of DNA damage compared with the control group. While co-treated groups with rifampicin and curcumin revealed a considerable ameliorative effect in comet tail length and % of DNA damage in group C and D compared with control one.

Fig. (1): photomicrograph with florescent microscope showing the effect of administration of curcumin(175 mg/kg b.wt with RIF(80 mg/kg b.wt) for four weeks on The oxidative DNA damage (comet assay) of the liver tissue of male mice.

GA: control group, GB: RIF treated group, GC: RIF + curcumin, GD: curcumin then RIF + curcumin

Genes Expressions

1- glutathion –s- transferase α2
Figure(2): The electrophotograph of glutathione-s-transferase α2 (450bp) mRNA expression in the liver tissue of male mice.

M: 100bp-1000bp DNA-ladder, 1: Group A: Male mice (Control).
2: Group B: Male mice treated with rifampicin.
3: Group C: Male mice co-treated with rifampicin and curcumin.
4: Group D: Male mice treated with curcumin one week prior rifampicin and curcumin co-treatment.

- The liver tissue of male mice show a decrease in the level of gene expression of glutathione-s-transferase α2 in the group (B) when compared with control one, while the level increased in group (C) than GB and there are drastic increase in the expression level in GD.

2- glutathione-s-transferase mu2

Figure(3): The electrophotograph of glutathione-s-transferase mu2 (230bp) mRNA expression in the liver tissue of male mice.

M: 100bp-1000bp DNA-ladder. 1: Group A: Male mice (Control).
2: Group B: Male mice treated with rifampicin.
3: Group C: Male mice co-treated with rifampicin and curcumin.
4: Group D: Male mice treated with curcumin one week prior rifampicin and curcumin co-treatment.

- The liver tissue of male mice showed a decrease in the level of gene expression of glutathione-s-transferase mu2 in the group (B) when compared with control one, while the level increased in group (C) than GB but not reach to the control group, and there was a drastic increase in the expression level in GD become more than the expression level in the control group.

3- Catalase

Figure(4): The electrophotograph of catalase (548bp) mRNA expression in the liver tissue of male mice.
M: 100bp-1000bp DNA-ladder. 1: **Group A**: Male mice (Control).
2: **Group B**: Male mice treated with rifampicin.
3: **Group C**: Male mice co-treated with rifampicin and curcumin.
4: **Group D**: Male mice treated with curcumin one week prior rifampicin and curcumin co-treatment.

- The liver tissue of male mice show a decrease in the level of gene expression of catalase in the group (B) when compared with control one, while the level increased in (GC) and (GD) than (GB).

**4- 8-oxoguanine DNA-glycosylase 1(OGG1)**

Figure(5): The electrophotograph of 8-oxoguanine DNA-glycosylase 1 (320bp) mRNA expression in the liver tissue of male mice.

M: 100bp-1000bp DNA-ladder. 1: **Group A**: Male mice (Control)
2: **Group B**: Male mice treated with rifampicin.
3: **Group C**: Male mice co-treated with rifampicin and curcumin.
4: **Group D**: Male mice treated with curcumin one week prior rifampicin and curcumin co-treatment.

- The liver tissue of male mice showed an elevation in the level of gene expression of 8-oxoguanine DNA-glycosylase 1(OGG1) in the group (B) when compared with control one, while the level decreased in group (C) than GB and there are drastic decrease in the expression level in GD.

**5- Cytochrome P450IIE1**

Figure(6): The electrophotograph of cytochrome P450IIE1 (280bp) mRNA expression in the liver tissue of male mice.

M: 100bp-1000bp DNA-ladder. 1: **Group A**: Male mice (Control)
2: **Group B**: Male mice treated with rifampicin.
3: **Group C**: Male mice co-treated with rifampicin and curcumin.
4: **Group D**: Male mice treated with curcumin one week prior rifampicin and curcumin co-treatment.

- The liver tissue of male mice showed a demarcated increase in the level of gene expression of cytochrome P450IIE1 in the group (B) when compared with control one, While in groups co-treated with rifampicin and curcumin (GC and GD) the level of expression is more or less similar to control group.

**6- GAPDH:**
4. Discussion

Rifampicin, being the first line drug used as antituberculous chemotherapy, is known to be associated with hepatotoxicity. (Tasduq et al., 2005). Rifampicin mediated oxidative damage is generally attributed to the formation of the highly reactive oxygen species, which act as stimulators of lipid peroxidation and source for destruction and damage to the cell membrane (Georgieva et al., 2004). The effect of rifampicin on DNA in the present study was confirmed by determination of serum level of 8 hydroxy 2’ deoxy guanosine (8OH2dG) and the comet assay protocol on the liver tissue of male mice. 8-hydroxydeoxyguanosine is a nucleotide form that results from oxidative DNA damage, which causes mutation in vitro and in vivo. So the occurrence of 8-OHdG (8-hydroxy-2’deoxyguanosine) has been used to study damaging effects on DNA of ROS. Results of many studies (Kassie et al., 2001 and Yamauchi et al., 2004), conducted thus far indicate that 8-OHdG is a sensitive biomarker to asses the extent of DNA damage and repair in both clinical and occupational settings. Our results show that there was a very high significant increase of serum level of 8 hydroxy 2’ deoxy guanosine (8OH2dG) in rifampicin treated group when compared to the control group, while the level of (8OH2dG) show a drastic decrease in rifampicin co-treated group and the decrease in serum level become nearly around the control group in curcumin pre treated group.

due to the ability of ROS to induce DNA damage via causing DNA-protein cross links and modifications of base residues such as introduction of a hydroxyl group (-OH) into the C-8 position of guanosine and guanine residues forming 8-OHdG and of DNA oxidation (Valko et al., 2006 and Iqbal et al., 2009).

The SCGE, also known as comet assay, is one of the recent methods established in order to detect different types of DNA damage. The comet assay has been established as a simple, rapid, cheap, flexible and, most importantly, sensitive method to detect DNA damage, which is also able to detect DNA damage in individual cells (Tice et al., 2008). The comet assay test is considered the most reliable and superior to other short term mutagenicity assays (Gollapudi and McFadden, 1995). So we select the test for studying genotoxicity of ciprofloxacin than other genotoxicity assays (e.g. micronuclei, mutations,structural chromosomal abrrations) and the technique used to detect the DNA damage for the previous mentioned comet technique advantages. Our result revealed that administration of rifampicin caused an increase in DNA oxidative damage in liver of male mice indicated by the damaged nuclei (comet tail length and % of DNA damage). rifampicin caused very high significant increase in comet tail length and % of DNA damage compared with the control group. While co-treated groups with rifampicin and curcumin revealed a considerable ameliorative effect in comet tail length and % of DNA damage in group C and D compared with rifampicin treated group.

Aly and Donya, 2002 concluded that RIF is a somatic and germ cell mutagen. It induced a dose dependent increase in the percentage of chromosome aberrations in mouse bone marrow after treatment with single and repeated therapeutic doses of RIF. The drug increased sister-chromatid exchanges in mouse bone marrow cells and induced chromosome abnormalities in mouse spermatocytes.

Awodele et al., 2010 suggested that rifampicin has a damaging effects on the DNA which evaluated by using micronucleus assay and this damage may be induced by free radicals generated by this drug.

Regarding to the oxidative stress related to rifampicin, The liver tissue of male mice in our experiment showed a decrease in the level of gene expression of anti oxidant enzymes (glutathion s transferase α2, glutathion s-transferase mu2 and
catalase) in the rifampicin treated group when compared with control one, while the level increased in rifampicin co-treated group than rifampicin treated group but not reach to the control group, and there was a drastic increase in the expression level in curcumin pre-treated group, become more than the expression level in the control group.

A successful model of hepatotoxicity was produced by giving 50 mg/kg/day each of INH and RMP in two weeks. Liver showed type II hepatocellular changes (microvesicular fat deposition) with mild portal triaditis. The glutathione and related thiol were significantly decreased in both blood and liver tissues with combination of INH and RMP treatment. Superoxide dismutase, glutathione peroxidase, catalase and glutathione-S-transferases were decreased in the treated group. The altered profile of antioxidant enzymes with increased lipid peroxidation indicated the enhanced oxidative-stress in combination of INH and RMP treatment. Thus the hepatotoxicity of INH and RMP is appeared to be mediated through oxidative-stress. (Sodhi et al., 1997).

It was found that the administration of antidotal therapy with curcumin greatly improved the gene expression of antioxidant enzymes; this may be due to the antioxidant effect of Curcumin. The antioxidant mechanisms of curcumin have recently been the focus of interest of free-radical chemists and biologists. Curcumin is known to protect biomembranes against oxidative damage. Peroxidation of lipids is known to be a free-radical-mediated chain reaction, leading to the damage of the cell membranes, and the inhibition of peroxidation by curcumin is mainly attributed to the scavenging of the reactive free radicals involved in the peroxidation. Most of the antioxidants have either a phenolic functional group or a B-diketone group. Curcumin is an unique antioxidant, which contains a variety of functional groups, including the B-diketo group, carbon–carbon double bonds, and phenyl rings containing varying amounts of hydroxyl and methoxy substituents (Wright, 2002).

(Ricky et al., 2001) suggest that Curcumin prevents colon cancer in rodent models. It inhibits lipid peroxidation and cyclooxygenase-2 (COX-2) expression and induces glutathione S-transferase (GST) enzymes. They tested the hypothesis that 14 days of dietary curcumin (2%) affects biomarkers relevant to cancer chemoprevention in the rat. The curcumin increased hepatic GST by 16% when compared with controls.

Our result showed that the liver tissue of male mice has an elevation in the level of gene expression of 8-oxoguanine DNA-glycosylase 1 (OGG1) in the rifampicin treated group when compared with control one, while the level decreased in groups co-treated with curcumin (and there are a clear decrease in the expression level in curcumin pre-treated group).

Regarding to DNA oxidation, when persistent during replication of DNA, can lead to mutations, Owing to the significance of DNA oxidative damage for the integrity of DNA, extensive DNA repair pathways have evolved (Lindahl and Wood, 1999). Even for the 8-oxo-dG lesion redundancy exists The human repair enzyme 8-oxo-G-DNA glycosylase (OGG)-1 gene has recently been cloned, (Hazra et al., 1998).

Our result showed that the liver tissue of male mice showed a demarcated increase in the level of gene expression of cytochrome P450IIE1 in the rifampicin treated group when compared with control one. While in groups co-treated with rifampicin and curcumin (GC and GD) the level of expression is more or less similar to control group.

Anti-tuberculosis drugs act as inducers of hepatic cytochrome P450 enzymes. For example, rifampicin is a potent inducer of CYP2D6 and CYP3A4, and isoniazid induces CYP2E1 in human (Vuilleumier et al., 2006). The induction of CYT P450 enzymes is known to take part in increased drug disposition and development of multi-drug resistance. Xenobiotics, including anti-tuberculosis drugs, undergo biotransformation in the liver catalyzed by microsomal enzyme systems. The major isozyme of cytochrom P450 enzymes in bioactivation is CYT2E1, which is also involved in hepatic toxicity of carbon tetrachloride, ethanol and acetaminophen. Inhibition of this isozyme by specific inhibitors or herbal drugs has been shown to be hepatoprotective (Bradford et al., 2005).

Conclusions
From previous investigations and the evidence of oxidative stress of rifampicin, antitubercular antibiotic, it can be concluded that it induce liver injury and oxidative DNA damage. These harmful effects greatly imply the beneficial role of our study to ameliorate these harmful effects. The use of curcumin demonstrate it is beneficial effects against rifampicin induced liver genotoxicity and curcumin ameliorate the deleterious effects of oxidative stress and it may be not only curcumin is beneficial against rifampicin-induced hepatic genotoxicity, but also as prophylactic measure

Acknowledgements
The author would like to thank members of Biochemistry Department, Faculty of Veterinary Medicine, Zagazig University, Egypt for their valuable help, support and for allowing access to their facilities which meant our work could be conducted in optimum conditions.
References


2/11/2013