Berberine Attenuates Isoniazid-Induced Hepatotoxicity by Modulating Peroxisome Proliferator-Activated Receptor γ, Oxidative Stress and Inflammation

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Abstract: The antituberculosis drug-induced hepatotoxicity is a leading cause of liver injury in many countries. The current study aimed to investigate the possible protective effects of the isoquinoline alkaloid berberine against isoniazid (INH)-induced hepatotoxicity in rats. The experimental rats received 100 mg kg⁻¹ b.wt. INH and concurrently administered berberine at doses of 25 and 50 mg kg⁻¹ orally for 45 days. To evaluate the hepatoprotective effects of berberine, serum markers of the liver function, serum pro-inflammatory cytokines and liver oxidant/antioxidant biomarkers were assayed. In addition, gene expression levels of inducible nitric oxide synthase (iNOS), nuclear factor-kappa B (NF-κB) and peroxisome proliferator-activated receptor gamma (PPARγ) were determined. INH-induced hepatic damage evidenced by the significantly elevated serum transaminases, serum pro-inflammatory cytokines and liver lipid peroxidation and nitric oxide levels. Consequently, serum albumin, liver glutathione and activities of the antioxidant enzymes were significantly declined. Further, INH administration produced a significant upregulation of liver iNOS and NF-κB and downregulation PPARγ mRNA expressions. Concurrent supplementation of berberine restored the altered markers to an almost normal state, in a dose-dependent manner. In conclusion, Berberine protects against INH-induced oxidative stress and inflammation leading to liver injury. The protective effects of berberine can be attributed to its ability to upregulate PPARγ and subsequently suppress NF-κB, iNOS and release of the pro-inflammatory cytokines.

Key words: Isoniazid, berberine, hepatotoxicity, PPARs, oxidative stress, inflammation

INTRODUCTION

Liver plays a critical role in the detoxification and excretion of several drugs and any injury or impairment of its functions may lead to many complications in the body (Sapkal et al., 2008). Hepatotoxicity represents the most important reason for the non-approval and withdrawal of drugs by the Food and Drug Administration (Mahmoud, 2014). In this regard, the antituberculosis drug-induced liver injury is the most frequent hepatotoxicity in many countries (Huang, 2014). Among the antituberculosis drugs, isoniazid (INH) has been reported to be the drug that most frequently induces hepatotoxicity (Metushi et al., 2011). Although INH is associated with a high incidence of liver injury (Metushi et al., 2011), it remains a widely used and efficient first-line agent for the treatment of tuberculosis (Koul et al., 2011).

Berberine (BBR) is an isoquinoline alkaloid present in many medicinal plants, such as Berberis vulgaris, Hydrastis canadensis, Coptidis rhizoma and Berberis aristata (Tang et al., 2009). Recently, berberine has been used for cancer therapy as well as cardiovascular, endocrine and nervous system diseases (Kulkarni and Dhir, 2010; Vuddanda et al., 2010; Zhang et al., 2011). Multiple studies have revealed that berberine possesses a wide range of pharmacological activities, including anti-inflammatory (Kuo et al., 2004; Germoush and Mahmoud, 2014), antioxidant (Yokozawa et al., 2004) and antidiabetic effects (Wang et al., 2011). In addition, clinical trials demonstrated that berberine is a safe oral hypoglycemic drug to treat dyslipidemic type 2 diabetic patients (Yin et al., 2008; Zhang et al., 2008).

Nuclear receptors have been reported to be potential targets of berberine (Guo et al., 2011). Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors belonging to the nuclear receptor superfamily, which additionally involves the steroid and thyroid hormone receptors (Decker et al.,

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2008; Soldo-Juresa and Metelko, 2009). It has been reported that dysregulations of specific PPAR isoforms contribute to the development of a wide range of liver diseases (Peyrou et al., 2012). In addition, Marra et al. (2000) and Zhang et al. (2012) revealed that PPARγ deficiency in hepatic stellate cells is associated with excessive formation of fibrotic tissue in the liver. Recent studies reported that berberine increases expression of PPARα in diabetic rat retina (Zhou and Zhou, 2007) and inhibits the expression of inflammatory cytokines in acetylated low-density lipoprotein-stimulated macrophages through PPARγ pathway (Chen et al., 2008).

To the best of our knowledge, the involvement of PPARγ in the protective effect of berberine against INH-induced liver injury has not been previously investigated. Therefore, the current study was undertaken to investigate the protective efficacy of berberine against INH-induced hepatotoxicity in rats, especially to modulation of hepatic PPARγ expression, oxidative stress and inflammation.

MATERIALS AND METHODS

Drugs and reagents: Berberine chloride, glutathione (GSH), pyrogallol, thiobarbituric acid (TBA) and 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) were purchased from Sigma Company (USA). Isoniazid was supplied from Fluka Company (Germany) and all other chemicals were of analytical grade and obtained from standard commercial supplies.

Experimental animals: White male albino rats weighing about 130-150 g obtained from the animal house of the National Research Centre (El-Dokki, Giza, Egypt), were used as experimental animals in the current investigation. The animals were housed in standard polypropylene cages (4 rats per cage) at normal atmospheric temperature (25±5°C) and normal 12 h light/dark cycle. Rats were fed a standard laboratory diet of known composition and water ad libitum. All animal procedures were approved by the Institutional Ethics Committee of Beni-Suef University, which confronted to the recommendations of the CCAC (1993).

Experimental design: Animals were allocated randomly into 4 experimental groups, each comprising 6 rats and subjected to the following treatments:

Group 1 (Control): Served as control rats and were orally administered 0.5% carboxymethylcellulose (CMC) (5 mL kg⁻¹ b.wt.) throughout the experimental period.

Group 2 (INH): Rats received 100 mg kg⁻¹ INH (Shoba et al., 2008) and 0.5% CMC orally for 45 days.

Group 3 (INH+25 mg BBR): Rats received 100 mg kg⁻¹ INH and 25 mg kg⁻¹ BBR (Bhutada et al., 2011) suspended in 0.5% CMC orally for 45 days.

Group 4 (INH+50 mg BBR): Rats received 100 mg kg⁻¹ INH and 50 mg kg⁻¹ BBR (Germoush and Mahmoud, 2014) suspended in 0.5% CMC orally for 45 days.

The doses were adjusted every week as indicated by any change in body weight to keep up similar dose per kg body weight of rats over the entire period of the study. At the end of the treatment period, rats were sacrificed under anaesthesia 24 h after the last treatment.

Sample preparation: Blood samples were collected, left to coagulate and centrifuged at 3000 rpm for 15 min to separate serum. Liver samples were immediately excised and perfused with ice-cold saline. Frozen liver samples (10% w/v) were homogenized in chilled saline and the homogenates were centrifuged at 3000 rpm for 10 min. The clear homogenates were collected and used for subsequent assays.

Biochemical study

Assay of liver function markers: Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were determined according to the method of Schumann and Klaue (2003) using reagent kits purchased from Biosystems (Spain). Serum alkaline phosphatase (ALP) activity was measured according to the method of Wenger et al. (1984) using Spireact (Spain) reagent kit. Serum total bilirubin and albumin levels were assayed following the methods of Kaplan and Pesce (1984) and Webster (1974) using reagent kits supplied by Spireact (Spain).

Assay of serum cytokines: Serum levels of tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) were determined using specific ELISA kits (R & D systems) following the manufacturer’s instructions. The concentrations of assayed cytokines were measured spectrophotometrically at 450 nm. Standard curves were constructed by using standard cytokines and concentrations of the unknown samples were determined from the standard plots.

Assay of oxidative stress and antioxidant defense system: Liver lipid peroxidation content was assayed by measurement of malondialdehyde (MDA) formation.
according to the method of Preuss et al. (1998). Nitric Oxide (NO) was determined according to the method of Montgomery and Dymock (1961) using reagent kit purchased from Biodiagnostics (Egypt). Reduced glutathione (GSH) content and activities of the antioxidant enzymes, superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), were measured according to the methods of Beutler et al. (1963), Marklund and Marklund (1974), Cohen et al. (1970) and Kar and Mishra (1976), respectively.

**RNA isolation and quantitative polymerase chain reaction (qPCR):** Gene expression analysis was performed as we previously described (Mahmoud, 2014). Briefly, total liver RNA was isolated using Fermentas RNA isolation kit and concentrations were quantified at 260 nm. RNA samples with A260/A280 ratios of more than 1.6 were selected. Reverse transcription of RNA to cDNA was performed with 1 μg RNA using reverse transcription kit (Fermentas). Synthesized DNA was amplified by CYBR Green master mix (Fermentas) in a total volume of 20 μL using the primer set described in Table 1. Reactions were seeded in 96-well plate and the PCR cycles included initial denaturation at 95°C for 10 min and 35 cycles of denaturation at 95°C for 30 sec, annealing for 30 sec and extension at 72°C for 30 sec. The obtained amplification data were analysed by the 2^ΔΔCt (Livak and Schmittgen, 2001) and the values were normalized to β-actin.

**Statistical analysis:** Data were analysed using SPSS v.16 and all statistical comparisons were made by means of the one-way ANOVA test followed by Turkey’s test post hoc analysis. Results were articulated as Mean±Standard Error (SE) and a p-value<0.05 was considered significant.

**RESULTS**

Data summarized in Table 2 showed that INH administration to rats produced a significant (p<0.001) increase in serum ALT, AST and ALP activities when compared with the corresponding normal control rats. On the other hand, concurrent supplementation of either doses of berberine markedly alleviated serum ALT (p<0.001), AST (p<0.01) and ALP (p<0.01) activities.

Similarly, INH-administered rats exhibited significantly (p<0.01) elevated serum total bilirubin levels when compared with the normal control ones. Both doses of berberine produced a significant (p<0.05) decrease in bilirubin levels, as represented in Table 2. By comparison with the control rats, serum albumin concentration of INH-administered rats showed a significant (p<0.05) decline. The 50 mg dose of berberine significantly (p<0.05) ameliorated serum albumin levels when compared with the INH control rats. In contrast, the effect of the lower berberine dose on serum albumin was non-significant (p>0.05), as depicted in Table 2.

Serum levels of the pro-inflammatory cytokines, TNF-α and IL-1β, were significantly (p<0.001) elevated in INH-administered rats compared with the normal controls (Table 3). Both the 25 and 50 mg doses of berberine potentially (p<0.001) decreased the elevated TNF-α and IL-1β levels when concurrently administered with INH. The 50 mg berberine seemed to be more effective in reducing serum TNF-α (p<0.05) when compared with the lower dose.

In addition, INH administration produced a significant (p<0.001) increase in liver lipid peroxidation and NO levels, as represented in Fig. 1 and 2, respectively. Concurrent administration of berberine potentially (p<0.001) decreased the elevated liver MDA and NO when compared with the INH control rats. Although both berberine doses have more or less similar effects, the 50 mg dose seemed to be more effective in decreasing liver MDA and NO levels.

Liver GSH exhibited a different pattern (Fig. 3); it was significantly (p<0.05) decreased in INH-intoxicated rats and the 25 mg as well as the 50 mg doses of berberine markedly (p<0.05) improved its levels. In the same context,

<table>
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<th>Primers 5'-3'</th>
<th>Gene bank accession number</th>
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<tr>
<td>PPARγ</td>
<td>NM_001145567.1</td>
<td>UP: GGGCAGCTGAAGAAGAGACCTG</td>
</tr>
<tr>
<td>Down: CGGGTCTGCTGCTGATAGT</td>
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<tr>
<td>iNOS</td>
<td>U00699.1</td>
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<td>Down: GCACCTTGGCTCAGGATTTCT</td>
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<tr>
<td>NFκB</td>
<td>AF0739381.4</td>
<td>UP: TCTCAGCTCGAACCAGTCG</td>
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<td>Down: TGGGTCTGTGTTAGATCTCC</td>
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<td>β-actin</td>
<td>NM_031144.3</td>
<td>UP: TACAACTCTTGTGACATTCTT</td>
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<td>Down: CCTCTGAGCCATACCACC</td>
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<table>
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<tr>
<th>Parameters</th>
<th>ALT</th>
<th>AST (μL⁻¹)</th>
<th>ALP (μL⁻¹)</th>
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<tr>
<td>Control</td>
<td>26.58±2.41</td>
<td>44.05±3.57</td>
<td>51.66±3.57</td>
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<tr>
<td>INH</td>
<td>81.45±5.55***</td>
<td>109.60±8.17***</td>
<td>122.84±8.53***</td>
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<tr>
<td>INH+25 mg BBR</td>
<td>45.85±4.56***</td>
<td>65.17±6.92***</td>
<td>72.22±6.19***</td>
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<tr>
<td>INH+50 mg BBR</td>
<td>41.59±2.82***</td>
<td>66.21±3.74***</td>
<td>67.16±4.72***</td>
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Data is expressed as Mean±SE *p<0.05, **p<0.01, ***p<0.001 vs. control and #p<0.05, ##p<0.01, ###p<0.001 vs. INH
Fig. 1: Liver lipid peroxidation in control, INH and INH+BBR rats. Data is expressed as Mean±SE, ***p<0.001 vs. control and ###p<0.001 vs. INH.

Fig. 2: Liver nitric oxide in control, INH and INH+BBR rats. Data is expressed as Mean±SE. ***p<0.001 vs. control and ###p<0.001 vs. INH.

Table 3: Serum markers of liver function in control, INH and INH+BBR rats

<table>
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<tr>
<th>Groups</th>
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<tr>
<td></td>
<td>TNF-α (μg mL⁻¹)</td>
<td>IL-1β (μg mL⁻¹)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>36.15±4.38</td>
<td>27.48±2.30</td>
<td></td>
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<tr>
<td>INH</td>
<td>100.40±3.04***</td>
<td>77.84±4.45***</td>
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<tr>
<td>INH+25 mg BBR</td>
<td>56.17±4.70***</td>
<td>34.25±2.97***</td>
<td></td>
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<tr>
<td>INH+50 mg BBR</td>
<td>38.08±2.98***</td>
<td>25.88±2.89***</td>
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</tr>
<tr>
<td>F-prob</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td></td>
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</table>

Data is expressed as Mean±SE. *p<0.05, ***p<0.001 vs. control, ###p<0.001 vs. INH and #p<0.05 vs. INH+25 mg BBR.

INH-intoxicated rats exhibited significantly reduced activities of liver SOD (p<0.01), CAT (p<0.001) and Gpx (p<0.05) when compared with their respective control rats. Concurrent administration of the 25 mg berberine dose along with INH significantly (p<0.05) alleviated the altered liver antioxidant enzymes activity. Likewise, the 50 mg berberine produced more or less similar effects where it increased the activities of SOD (p<0.05), CAT (p<0.001) and Gpx (p<0.01) as depicted in Fig. 4-6.

Fig. 3: Liver reduced glutathione content in control, INH and INH+BBR rats. Data is expressed as Mean±SE, *p<0.05 vs. control and #p<0.05 vs. INH.

Fig. 4: Liver superoxide dismutase activity in control, INH and INH+BBR rats. Data is expressed as Mean±SE, ***p<0.01 vs. control and *p<0.05 vs. INH.

Fig. 5: Liver catalase activity in control, INH and INH+BBR rats. Data is expressed as Mean±SE, ***p<0.001 vs. control, *p<0.05, ***p<0.001 vs. INH and #p<0.05 vs. INH+25 mg BBR.

Data concerning the gene expression levels assessment in the liver of control and experimental
animals were represented in Fig. 7-9. INH-administered rats exhibited a significant upregulation of liver iNOS (p<0.01) and NF-κB (p<0.001) mRNA expressions when compared with the normal control rats. Treatment of INH-intoxicated rats with either the 25 or 50 mg berberine doses markedly decreased liver iNOS (p<0.05) and NF-κB (p<0.001) mRNA expression levels as depicted in Fig. 7 and 8, respectively. On the contrary, PPARγ expression in the liver of INH-administered rats showed a significant (p<0.05) downregulation compared with the normal control rats (Fig. 9). Berberine, at dose level of 25 mg, significantly (p<0.01) upregulated liver PPARγ mRNA expression. The higher berberine dose noticeably increased liver PPARγ mRNA expression when compared with the INH (p<0.001), INH+25 mg BBR (p<0.01) and normal control (p<0.001) groups.

DISCUSSION

Isoniazid remains the mainstay first-line drug for the treatment of tuberculosis in spite of its association with a high incidence of liver injury and even liver failure (Center for Disease Control and Prevention, 2010; Metushi et al., 2011). Isoniazid is first metabolized by N-acetyltransferase (NAT) to acetylisoniazid then hydrolysed to acetylhdyrazine (Huang et al., 2002). Acetylhdyrazine can be oxidized by cytochrome P450 2E1 (CYP2E1) to many hepatotoxic intermediates. In addition, isoniazid may be directly hydrolyzed by amidease to potent toxic hydrazine (Huang, 2007). Acetylhdyrazine has been reported to be a toxic metabolite that can bind covalently to liver proteins in vivo (Timbrell et al., 1980). Further, Vuilleumier et al. (2006) demonstrated that hydrazine is predominantly responsible for isoniazid-induced hepatotoxicity. Therefore, the current study was undertaken to investigate the protective efficacy of berberine against isoniazid-induced hepatotoxicity in rats. We thought that the beneficial effects of berberine might
be mediated through modulation of PPARγ expression and attenuation of inflammation and oxidative stress.

Isoniazid administration to rats produced liver injury evidenced by the elevated circulatory aminotransferases and bilirubin levels with a concomitant decrease in serum albumin concentration. The elevated aminotransferases are indicative of the induced hepatocellular damage (Kumar et al., 2005) and the fall in serum albumin is a consequence of decreased synthetic capability due to liver damage (Sherlock and Dooley, 2002). On the other hand, concurrent administration of berberine markedly ameliorated the altered serum markers of liver function. In consistent with our findings, studies showed that berberine decreased serum aminotransferases in carbon tetrachloride (CCL4)-intoxicated mice (Dmitrovic et al., 2013) and in cyclophosphamide (CP)-induced hepatotoxicity in rats (Germoush and Mahmoud, 2014), confirming its hepatoprotective and membrane stabilizing efficacies.

Oxidative stress has been implicated in the antitubercular drug induced hepatotoxicity (Sodhi et al., 1997). A growing body of evidence also suggests that idiosyncratic drug-induced liver injury may be mediated, at least in part, by oxidative stress (Boelsterli, 2002; Tafazoli et al., 2005). Under oxidative stress conditions, Reactive Oxygen Species (ROS) induce lipid peroxidation, protein damage and DNA fragmentation (Perry et al., 2000; Nencini et al., 2007). In addition, ROS activate cell signaling pathways mediated by NFκB, mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) as reported by Martindale and Holbrook (2002) and Czaja (2007). The present study confirms previous observations (Palansamy and Manian, 2012) by showing that isoniazid induced a significant increase in liver lipid peroxidation levels. Similarly, isoniazid administration induced a significant increase in liver NO levels as a consequence of upregulated iNOS mRNA expression. iNOS has been reported to be upregulated in response to stress, catalysing NO production (Forstermann and Sessa, 2012). At the cellular level, NO reacts with superoxide anions to produce the potent antioxidant peroxinitrite (McKim et al., 2003; Valko et al., 2007), stimulates TNF-α production from Kupffer cells (Matata and Galinanes, 2002) and impairs energetic metabolism (Beltran et al., 2000; Vieira et al., 2001; Hara et al., 2005), hence favouring cell death.

On the contrary, isoniazid-administered rats exhibited a significant decline in liver GSH content as well as activities of SOD, CAT and GPx. GSH is one of the most important antioxidants that protects cellular constituents against oxidative stress induced damage by reacting with oxidants or as a substrate for GPx (Franco et al., 2007). SOD, CAT and GPx are likewise providing a defense system against ROS (Swamy et al., 2010). The recorded depletion of GSH level and reduced activities of the antioxidant enzymes in the present study may be attributed to the scavenging of toxic radicals generated by isoniazid (Ergul et al., 2010; Palansamy and Manian, 2012).

Concurrent supplementation of berberine along with isoniazid markedly decreased liver NO and lipid peroxidation levels. On the other hand, berberine ameliorated liver GSH content and increased activities of SOD, CAT and GPx. Accordingly, Dmitrovic et al. (2013) and Germoush and Mahmoud (2014) demonstrated that berberine significantly decreased liver lipid peroxidation levels and alleviated the antioxidant defense system parameters in CCL4-administered mice and CP-intoxicated rats, respectively. In addition, the observed decline in NO levels in berberine treated rats is attributed to downregulation of liver iNOS mRNA expression. Hence, we assume that berberine exerted its protective effect against isoniazid-induced liver damage through inhibiting GSH depletion and potentiating the antioxidant defense enzymes.

Various inflammatory cytokines produced during drug induced liver injury have been reported to be involved in promoting tissue damage (Ishida et al., 2002). The present findings revealed a significant increase in serum levels of TNF-α and IL-1β in isoniazid-intoxicated rats. Many studies reported that these cytokines play a critical pathological role in liver necrosis, increase vascular permeability and mediate inflammatory cell activation and apoptosis of hepatocytes (Mohammed et al., 2004; Tarantino et al., 2010). IL-1β elicits potent pro-inflammatory actions through its binding to IL-1 receptor and subsequently activates the transcription factors of the NFκB family (Dimarellu, 2011). Upon binding to its receptor, TNF-α can activate the proapoptotic caspase cascade (Tacke et al., 2009). The elevated serum levels of these inflammatory mediators in isoniazid-administered rats may be attributed to the upregulation of liver NFκB by ROS (Czaja, 2007) and NO (Matata and Galinanes, 2002). NFκB is a transcription factor involved in controlling the expression of various genes including, TNF-α, IL-1β and cyclooxygenase-2 (Lawrence et al., 2001; Muriel, 2007). Oral supplementation of berberine potentially decreased the expression of NFκB and serum levels of TNF-α and IL-1β. Accordingly, we recently demonstrated that berberine significantly decreased liver inflammatory cytokines gene expression and subsequently decreased their serum levels in CP-induced liver injury in rats (Germoush and Mahmoud, 2014).
Moreover, the protective effect of berberine against isoniazid-induced liver injury may be explained, at least in part, via its ability to upregulate PPARγ expression in the liver. Previous studies showed that activated PPARγ undergoes conformational shift that allows decreasing the activity of NF-κB, activator protein 1 (AP-1), signal transducer and activator of transcription (STATs) and subsequently suppresses synthesis of iNOS (Pascual et al., 2005; Ogawa et al., 2005; Rodriguez-Calvo et al., 2008) and pro-inflammatory cytokines (Chinneti et al., 2006; De Bosscher et al., 2006). In addition, treatment with PPARγ agonists eliminates oxidative stress in rodents (Bagi et al., 2004; Dobrian et al., 2004; Houstis et al., 2006) and reduces generation of ROS and lipid peroxidation from leukocytes of obese human subjects (Garg et al., 2000). Marrella et al. (2006) reported that PPARγ activation lowers production of superoxide radicals from diabetic plaques and monocytes in diabetic patients. Furthermore, through PPARγ binding elements in the promoter region of their genes, PPARγ has been reported to upregulate the expression of CAT (Gimun et al., 2002; Okuno et al., 2008) and SOD (Gong et al., 2012) in rodents.

In conclusion, the current study provides novel information on the protective mechanism of berberine against isoniazid-induced hepatotoxicity. Our findings suggest that berberine, in a dose dependent manner, attenuates inflammation and oxidative stress induced by the isoniazid. Further, the hepatoprotective effect of berberine can be attributed to its ability to upregulate PPARγ and subsequently suppress NF-κB, iNOS and release of the pro-inflammatory cytokines.

REFERENCES


