

Original Research Article

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Protective Effect of Quercetin on Azithromycin Induced Hepatotoxicity and Nephrotoxicity in Wistar Rats

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ABSTRACT

Keywords

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The aim of this study was to investigate the possible protective role of flavonoid quercetin on azithromycin induced toxicity using biochemical and histopathological approaches. In experimental rats oral administration of azithromycin (30 mg/kg b.wt.) for 4 weeks significantly induced liver and renal damage which was evident from the significant ($P < 0.05$) increased levels of liver enzymes (AST and ALT) activities, total bilirubin and creatinine concentration. Moreover, the liver of azithromycin treated rats showed severe sinusoidal hemorrhages, congestion, vacuolar degeneration, fatty changes and disruption of hepatic cords were seen. The lesions in kidneys consisted of severe tubular and cortical hemorrhages, luminal cast formation and desquamous of tubular lining epithelium. Increased space between cardiac muscle fibers, severe hemorrhages and infiltration of inflammatory cells were seen in heart. Quercetin treatment markedly attenuated the azithromycin induced biochemical alterations in serum. Quercetin also ameliorated the azithromycin induced pathological changes when compared with azithromycin alone treated group. These data indicate that the natural dietary antioxidant quercetin had protective effect against azithromycin induced hepatotoxicity and nephrotoxicity in rats.

Introduction

Azithromycin is antibiotics with bactericidal and bacteriostatic activities and is frequently prescribed for the treatment of upper and lower respiratory tract, pharyngitis, tonsillitis, dermatological infections, streptococcal pharyngitis, urogenital infections, otitis media and sexually transmitted disease due to chlamydia and gonorrhea (Cunha, 1996, Duran *et al.*, 2000 and Holmes, 2005). Azithromycin is the best seller antibiotic in

the USA, ranked 15th among the mostly-prescribed medications. Even though rare incidence of cardiotoxicity (Giudicessi and Ackerman, 2013) and cardiac arrhythmias were reported when given by rapid intravenous administration or in overdose (Tilelli *et al.*, 2006). The effects of azithromycin on liver damage have been well documented in clinical studies (Er, 2010, Lockwood *et al.*, 2010). Interstitial nephritis (Mansoor *et al.*, 1993, Soni *et al.*, 2004) and chronic renal failure after the second

occurrence of acute interstitial nephritis have been reported in clinical studies of azithromycin (Persico *et al.*, 2011). Flavonoids are a group of natural antioxidants which are non-nutritive dietary components that are widely distributed in plants. Flavonoids affect basic cell function such as growth, differentiation and apoptosis, because of their radical scavenging activity and proposed to exert beneficial effects in cancer, cardiovascular disease and neurodegenerative disorders.

Quercetin is one of the most frequently studied bioflavonoid in the class of flavonols. Quercetin is natural flavonoid present in high concentration in herbal drugs, fruits and vegetables like apples, onion, potatoes, broccoli, tea, soybeans, red wine. It is demonstrating broad biopharmacological properties (Renugadevi and Prabu, 2010).

Quercetin is a more potent antioxidant than other antioxidant nutrients such as vitamin C, vitamin E and β -carotene on a molar basis (Rice-Evans *et al.*, 1995) and it causes cytoprotective effects which prevents endothelial apoptosis caused by oxidants, directly scavenging free radical and induces hepatoprotectivity effects (Choi *et al.*, 2003, Renugadevi and Prabu, 2010). It can chelate transition metal ions, including iron, thus preventing iron catalyzed fenton reaction (Ferrali *et al.*, 2000).

Epidemiological studies have suggested that the intake of food containing flavonoids may be associated with reduced risk of coronary heart disease, hyper cholesterolemia, atherosclerosis and heart failure (Hollman and Katan, 1999, Stoclet *et al.*, 2004). It is marketed as a diet supplement with antihistamine, anti-inflammatory, antiviral, immunomodulatory and antioxidant properties (Ross and Kasum, 2002). It also possesses anti tumoral, antifungal,

vasorelaxation activity on hippocampal neurons (Pu *et al.*, 2007). It scavenges superoxide in ischemia reperfusion injury (Huk *et al.*, 1998).

Materials and Methods

Drugs and Chemicals

Azithromycin dihydrate $\geq 98\%$ (HPLC) (Sigma-Aldrich) and quercetin were used in experiment. Carboxy Methyl Cellulose (CMC) was used as a vehicle to formulate the dose.

Animals

A total 40 Wistar rats of either sex weighing 250-350 g were procured from Jay Research Foundation, Vapi, Gujarat. The study was carried out after ethical approval by Institutional Animal Ethical Committee (IAEC) (No.064-VCN-VPP-2018). Rats were maintained in an environmentally controlled room at a temperature of $22 \pm 3^\circ \text{C}$ and relative humidity of 40 to 70 percent with natural light-dark cycle. The rats were acclimatized to laboratory conditions for ten days. The animals were housed, five number of same sex rats in polypropylene cage with solid bottom having autoclaved paddy husk as bedding materials. The experimental rats were fed on standard rodent pellet feed with *ad libitum* clean and filtered drinking water in polypropylene bottles.

Animal Experiment

The animals were randomly divided into four different groups with 5 male and 5 female rats in each group. The rats in group-I were orally administered 0.5 ml of Carboxy Methyl Cellulose (CMC) and served as control. The rats in group-II were administered azithromycin alone (30 mg/kg b.wt.) for the period of 4 weeks. The rats in group-III were

administered quercetin alone (50 mg/kg b.wt.) for the period of 4 weeks. The rats in group-IV administered azithromycin (30 mg/kg b.wt) and quercetin (50 mg/kg b.wt.) for the period of 4 weeks.

Rats were observed daily for abnormal clinical signs. For blood collection, rats were anaesthetized using chloroform. Blood sample were collected from retro orbital venous plexus using rat capillaries at 0, 15th, 28th day of experiment in plain vial for separation of serum sample (blood coagulate at room temperature followed by centrifugation at 1000 rpm for ten minutes at 4°C for serum separation) for serum biochemical estimations.

At the end of experiment, the rats were sacrificed by over dose of ether inhalation. A detailed necropsy examination of each rat of different groups was performed and liver, kidneys and heart dissected out and fixed in 10% neutral buffered formalin for histopathological examination.

Methods

Estimation of biochemical parameters

The levels of ALT, AST, Creatinine, Blood urea nitrogen (BUN), Total bilirubin and blood glucose were estimated with the help of semi-automatic biochemical analyzer (Micro lab Instrument, Model: ARX-3) using diagnostic kits as per kit literature (Brand: Randox, Manufacturer: Randox Laboratories Ltd).

Histopathological examination

The liver, kidneys and heart excised after necropsy. The tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5µm and were stained with hematoxylin and eosin. Hepatic tissues

showed severe sinusoidal hemorrhages, congestion, vacuolar degeneration, fatty changes and desruption of hepatic cords.

Tubular injury was defined as severe tubular and cortical hemorrhages, luminal cast formation and desquamous of tubular lining epithelium. Increase space between cardiac muscle fibers, severe hemorrhages and infiltration of inflammatory cells were seen in heart.

Statistical Analysis

All the data were expressed as mean (\pm SE) of a number of experiments (n=10). The statistical significance was evaluated by using SPSS 16.0 statistical software (SPSS, Inc., 2007). One-way analysis of variance (ANOVA) followed by Duncan's test was performed to determine intergroup differences. The criterion for statistical significance was $P < 0.05$.

Results and Discussion

The alteration value of ALT, AST, total bilirubin and creatinine in serum in control and experimental rats are shown in Table 1. A significant ($p < 0.05$) increase in level of ALT, AST, total bilirubin and creatinine was observed in serum of only azithromycin treated rats when compared with normal rats.

Administration of quercetin (50mg/kg per day) along with azithromycin significantly ($p < 0.05$) restored the levels of ALT, AST, total bilirubin and creatinine to near normal levels when compared with azithromycin alone treated rats (Fig.1 A, B, C and D).

Histopathological changes in the liver and kidney were evaluated as described in materials and methods and the results are presented in histopathological slides.

Table.1 Biochemical enzyme activities values in different treatment groups at different time intervals

Parameters Studied	Groups n=10	0 Day	15 Day	28 Day
AST (U/L)	Gr.1	77.72± 2.66	81.35 ^c ± 2.66	83.60^c ± 2.67
	Gr.2	78.28±2.79	157.19 ^a ± 7.07	194.18^a ± 6.86
	Gr.3	82.22±2.86	94.37 ^c ± 2.67	95.08^c ± 4.41
	Gr.4	83.08±2.05	136.37 ^b ± 5.08	148.73^b ± 4.21
ALT (U/L)	Gr.1	43.12±1.40	49.27 ± 2.58	51.93^b ± 1.78
	Gr.2	46.61±1.39	48.99 ± 1.50	60.60^a ± 3.54
	Gr.3	41.95±2.65	48.55 ± 3.07	52.05^b ± 1.89
	Gr.4	41.10±1.54	55.66 ± 4.84	54.35^{ab} ± 2.00
Total bilirubin (mg/dl)	Gr.1	0.70±0.05	0.71 ^b ± 0.07	0.70^b±0.09
	Gr.2	0.63±0.07	1.10 ^a ± 0.15	1.01^a±0.11
	Gr.3	0.56±0.08	0.64 ^b ± 0.04	0.62^b±0.12
	Gr.4	0.65±0.05	0.90 ^{ab} ± 0.10	0.77^{ab}±0.07
Creatinine (mg/dl)	Gr.1	0.63±0.07	0.63 ± 0.07	0.63^b ± 0.07
	Gr.2	0.46±0.10	0.82 ± 0.09	0.95^a ± 0.07
	Gr.3	0.63±0.06	0.77 ± 0.05	0.72^b ± 0.02
	Gr.4	0.58±0.08	0.59 ± 0.08	0.68^b ± 0.07

Note: Treatments bearing different superscripts in a column differ significantly at P <0.05 (DMRT).

*0 day= at initiation of dosing

Fig.1 Effect of quercetin on azithromycin induced changes in liver and kidneys enzymes: (A) AST,(B) ALT, (C) Serum creatinine and (D) Total bilirubin in Wistar rats. Values are mean ± SE for ten rats in each group. ^{a,b,c}Bars not sharing a common superscript letter (a,b,c) differ significantly at P <0.05 (DMRT)

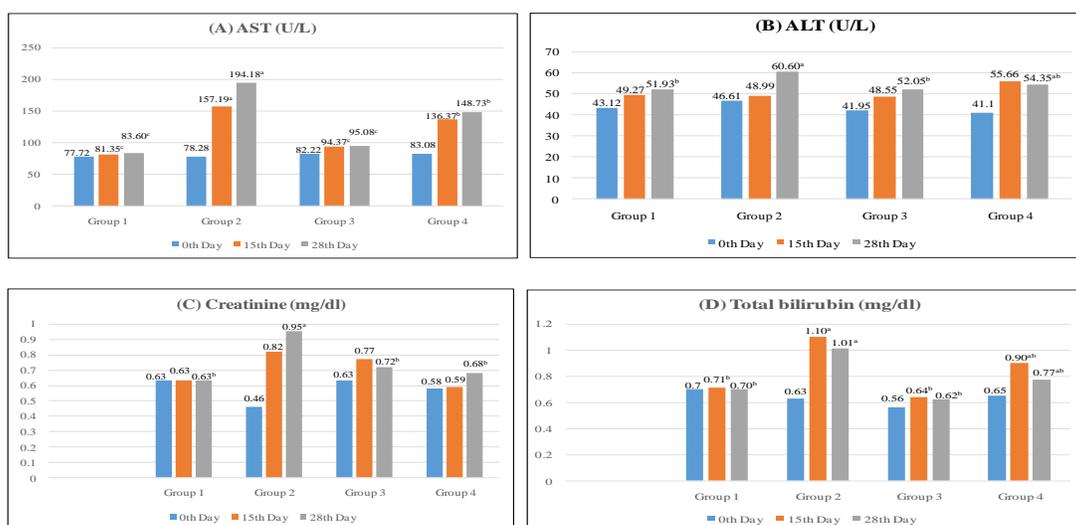
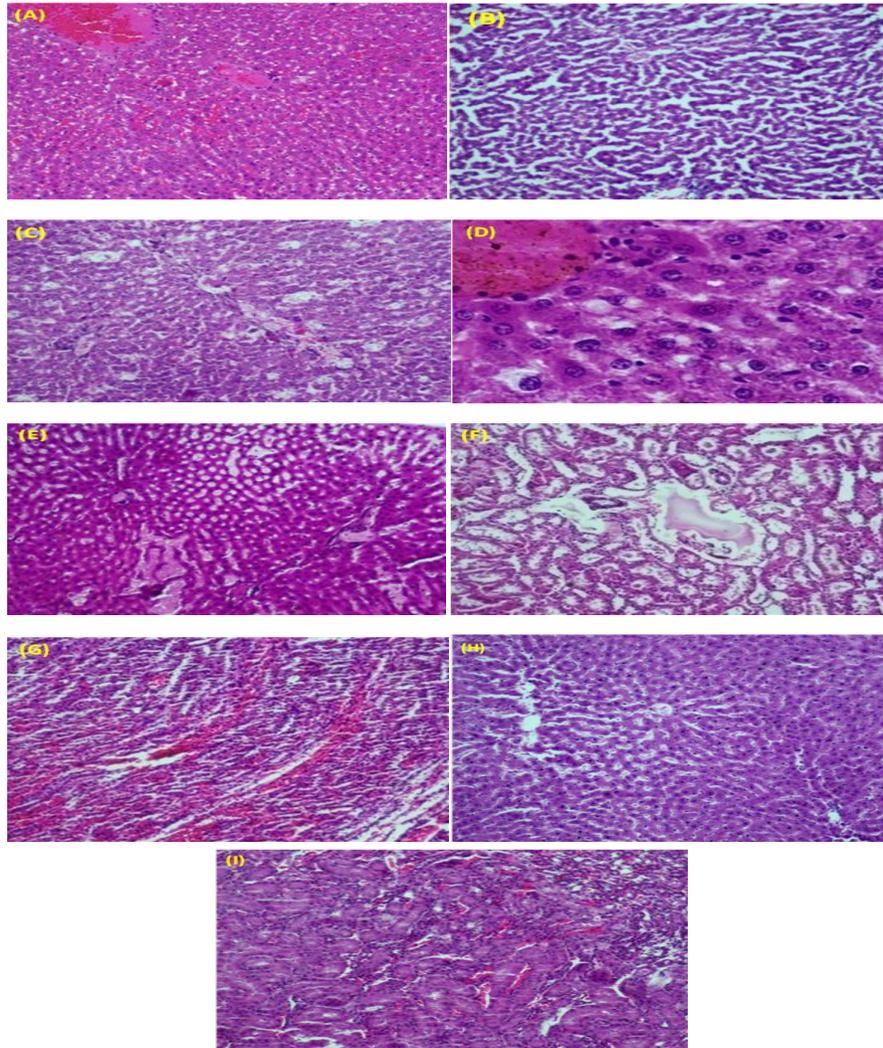


Fig.2 (A) Severe sinusoidal hemorrhages in liver, (B) Liver showing disruption of hepatic cord, (C) Mild infiltration of inflammatory cells in liver, (D) Liver showing vacuolated cytoplasm in hepatocytes, (E) Fatty changes in hepatocytes, (F) Luminal cast formation in kidney, (G) Severe hemorrhages in kidney, (H) Mild degenerative changes in liver after treatment with quercetin, (I) Mild hemorrhages and degenerative changes in kidney after treatment with quercetin



Treatment with azithromycin caused severe sinusoidal hemorrhages and congestion, disruption of hepatic cords, inflammatory cells infiltration, vacuolar degeneration and fatty changes. (Fig.2 A,B,C,D,E). In kidney azithromycin cause luminal cast formation severe tubular and cortical hemorrhages and desquamous of tubular lining epithelium (Fig.2 F,G). However treatment with quercetin ameliorated the hepatic and tubular (Fig.2 H,I). There were no histopathological

changes observed in rats treated with quercetin alone and in the control rats.

Azithromycin is frequently prescribed for the treatment of many infectious conditions. Azithromycin are lipophilic and are extensively distributed in body fluids and tissues and it exerts its antibacterial action, even though it affects liver, kidneys and heart. Hoe and Wilkinson (1973) reported that in the event of any cell wall damage, the

permeability of cell membrane either increased or the cell wall ruptured resulting in diffusion of the enzyme into the blood stream causing increased serum enzyme activity. The hepatotoxic effects of azithromycin appeared due to the generation of highly reactive free radicals because of oxidative threat caused by the drug which disrupted normal cellular functioning of the liver and kidney (Olayinka and Ore, 2014). In the present study increased activities of liver enzymes (AST and ALT) and total serum bilirubin concentration in serum of rats which attributed to the liver dysfunction. These results are in consistence with previous reports for drug induced liver toxicity (Cascaval and Lancaster, 2001; Chandrupatla *et al.*, 2002; Suriawinata and Min, 2002; Baciewicz *et al.*, 2005; Charest *et al.*, 2010; Das, 2011; Maggioli *et al.*, 2011; Olayinka and Ore, 2014; Martinez *et al.*, 2015 and Mobasher Ahmad *et al.*, 2018). However, Paulose *et al.*, (2016) reported liver ALT values were significantly decreased in azithromycin treated group, indicating the hepatotoxic potential of the antibiotic at 30mg/kg body weight because once the cell death happened, the source of enzyme declined.

Quercetin decreased the lipid peroxidation in the cell membranes (Gupta *et al.*, 2010) resulting suppresses the leakage of AST and ALT enzymes into blood circulation. In the present study reduced activities of liver enzymes (AST and ALT) by quercetin were reported. Similar to the present findings, Janbaz *et al.*, (2004); Chen (2010); Gupta *et al.*, (2010); Yousef *et al.*, (2010); De David *et al.*, (2011); Selvakumar *et al.*, (2012); Uzun and Kalender (2013); El Nekeety *et al.*, (2014) and Afifi *et al.*, (2018) also observed comparatively protective effect of quercetin. The hepatoprotective effect might be a result of the stabilization in the redox state and maintenance of the antioxidant capacity offered by quercetin. It could be also

attributed to calcium channel blocking activity exerted by quercetin (Kurose, 1981). Calcium contents in liver cells are liable to be increased during the process of experimental liver damage and calcium channel blocking drugs were found to inhibit the development of hepatic damage induced by different hepatotoxins (Thibault *et al.*, 1991). The hepatoprotective effect may be mediated through combination of multiple mechanisms, such as reported anti-oxidant, free radical scavenging, anti-inflammatory, calcium channel blocking and microsomal enzyme inhibitory action (Janbaz *et al.*, 2004).

Creatinine and urea are metabolic waste products that are freely filtered by the glomeruli of the kidneys (Gaspari *et al.*, 1998) and their serum/plasma concentrations are commonly used to screen for renal diseases (Ogawa, 1992 and Traynor *et al.*, 2006). Elevation of the plasma levels of creatinine and urea is an indication of abnormal renal function (Mouton and Holder, 2006). In present study serum concentration increased significantly in the azithromycin treated group of rats suggesting impairment of renal function. Whereas, BUN concentration did not show any significant variation. Increased serum creatinine concentration and BUN level observed by Soni *et al.*, (2004); Persico *et al.*, (2011); Olayinka and Ore (2014) and Mobasher Ahmad *et al.*, (2018). In this experiment quercetin significantly recovered the creatinine concentration in the serum of rats indicating its protective effect. Similar findings were also observed in previous studies (Renugadevi and Prabu, 2010; Yousef *et al.*, 2010 and Ilic *et al.*, 2014). The renal protection exerted by quercetin seems to be based on its ability to increase metallothionein in kidneys (Morales *et al.*, 2006). Metallothionein is a small cyteinerich protein that is induced by various stressors and it acts as a scavenger of heavy metals and as antioxidant. It is an efficient scavenger of

hydroxyl radicals and can functionally substitute for SOD in oxidative stress (Vicente-Sanchez *et al.*, 2008).

In conclusion, biochemical examination showed elevated liver and kidney enzymes and histopathological examination showed degenerative/necrotic changes, severe hemorrhages and vacuolar degeneration in liver; hemorrhages and degenerative changes in kidneys. These biochemical and histopathological changes improved by protective effect of quercetin at the dose rate of 50 mg/kg b.wt. in rats.

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