Effect of Flavonoid Quercetin Supplement on the Progress of Liver Cirrhosis in Rats

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Abstract: Liver cirrhosis is a serious health problem as it represents an irreversible stage of liver damage in both the developed and developing countries. Up till now no successful therapeutic approach has been developed for this disease. The objective of this study was to evaluate therapeutic efficacy of the flavonoid guercetin on liver cirrhosis induced by the hepatotoxin thioacetamide. Thirty male Albino rats weighing 160-200gm were randomly divided into 3 equal groups, Control group (C), Thioacetamide group (TA) treated with thioacetamide (100 mg/kg .i.p.) twice weekly for 6 weeks, Thioacetamide /Quercetin group (TA/Q) treated with thioacetamide (100 mg/kg .i.p.) twice weekly for 6 weeks as well as quercetin (50 mg/kg i.p.) for the last 3 weeks. After 6 weeks, all rats were sacrificed; blood samples were taken for determination of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilitubin, and adiponectin levels. Livers were weighed and were used for measurement of liver glutathione peroxidase (GPx), catalase (CAT), lipid peroxides and histopathological examination. TA rats showed significant increase of absolute and relative liver weights, liver peroxides, serum ALT, AST, ALP, and total bilirubin, while body weight, body mass index (BMI), Liver antioxidants (GPx, CAT) and serum adiponectin were significantly decreased compared to C rats. TA/Q group exhibited a decrease of liver peroxides, serum ALT, AST, ALP, and total bilirubin, while body weight, liver antioxidants (GPx, CAT) and serum adiponectin levels were significantly increased compared to TA group. Histopathological examination showed loss of normal liver architecture in TA rats (very thick septa and leukocytic infiltration). On the other hand, TA/O rat livers had almost normal hepatic architecture. In conclusion. The natural flavonoid guercetin could ameliorate thioacetamide induced - liver cirrhosis and dysfunction in adult rats.

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Key words: thioacetamide, liver cirrhosis, quercetin, lipid peroxides, liver antioxidants, serum liver enzymes, serum bilirubin.

Abbreviations: CYP2E : Cytochrome oxidase P450, 5HT :serotonin , MAPK: Mitogen-activated protein kinase, Akt: serine /threonine protein kinase , PI3- Kinase; Phosphoinositide 3-kinase. NF- κ B : nuclear factor kappa-light-chain-enhancer of activated B cells. TNF- α :Tumor necrosis factor α . TNF- β 1:Tumor necrosis factor- β 1 HSC :hepatic stellate cells. PPAR α : peroxisome proliferators activated receptor alpha. AMPK : 5'AMP-activated protein kinase

1. Introduction

Chronic liver injury in response to a variety of insults like alcohol abuse, drugs, metabolic diseases, and autoimmune attack on hepatocytes or bile duct epithelium eventually leads to liver fibrosis (Amalia *et al.*, 2007). Cirrhosis is a progressive hepatopathy constituting an irreversible stage of liver dysfunction (Amalia *et al.*, 2007). In Africa and Asia hepatitis B virus & hepatitis C virus are the leading causes of liver cirrhosis while in developed countries; it is most commonly linked to alcohol abuse (Fattovich *et al.*, 1997; Yu *et al.*, 2000 and Anthony. 2001).Although no successful therapeutic approach has been developed to this pathogenic process in liver disease. Yet, antioxidant therapies have been shown to achieve some positive effects (Pavanoto *et al.*, 2003). The hepatotoxin thioacetamide (TAA) was used in different doses to induce liver cirrhosis, severe bile duct proliferation and cholangiocarcinoma at longer intervals (Al-Bader et al., 2000). Liver damage is associated with biochemical changes in the form of higher baseline levels of total serum alkaline bilirubin, phosphatase, alanine aminotransferase, aspartate aminotransferase (Cucchetti et al., 2011) as well as histopathological changes in the form of mild vascular congestion and moderate inflammatory changes with congested sinusoids, nuclear changes, and centrilobular necrosis (Lim et al., 2010). Flavonoids are groups of more than 4000 polyphenolic compounds that occur naturally in foods of plant origin. These compounds possess a common phenylbenzopyrone structure (C6C3-C6), and they are categorized according to the saturation level and opening of the central pyran ring, mainly into flavones, flavanols, isoflavones, flavanones, and flavanonols (Masoodi and Alhamdanz, 2010). Human intervention studies have suggested beneficial effects of flavonoid-rich foods on biomarkers of inflammation and endothelial function (Landberg et al., 2011).Quercetin(3,5,7,3,4pentahydroxy flavon) is one of the most distributed flavonoids in human diet (Mink et al., 2007) which has been reported to function as carcinostatic, antiviral, inhibitor of platelet aggregation and oxidation of LDL, (Parl et al., 2003), cardioprotective and anti-inflammatory (Comalada et al., 2006). The present study aimed at investigating the effect of quercetin administration on the prognosis of chronic liver cirrhosis induced by thioacetamide in adult Swiss Albino rats.

2. Materials and Methods

The present study was approved by the Ethics Committee FMASU 936/2011

Experimental animals:

The present study was carried out on 30 adult male Swiss Albino rats weighing 160-200 gm at the start of the study. Rats were purchased from Ophthalmic Diseases Research Institute (Giza) and housed 3/cage in plastic cages and maintained in the Physiology Department Animal House under standard conditions of boarding at normal room temperature and in a controlled environment of 12h light /dark cycle with free access to water and rat chow. All rats were fed standard rat chow (AIN-93 M diet formulated for adult rodents) prepared according to the National Research Council (NRC) 1978 and Reeves *et al.* (1993).

Rats were randomly divided into three equal groups:

- 1-Group I;Control group (n= 10); C rats were given the vehicle at a dose of 1ml/Kg b.w.
- 2- Group II;Thioacetamide group (n=10); TA rats were treated with thioacetamide in a dose of 100 mg/kg b.w. dissolved in 1 ml distilled water, twice weekly for 6 weeks intraperitoneally (Apte *et al.* 2003).
- 3-Group III; Thioacetamide /quercetin group (n=10); TA/Q rats were treated with thioacetamide in a dose of 100 mg/kg b.w. dissolved in 1 ml distilled water twice weekly for 6 weeks. Quercetin was given daily for the last 3 weeks in a dose of 50 mg/kg b.w. dissolved in 1 ml of 1% methyl cellulose, intraperitoneally (Tieppo *et al.*, 2007).

Thioacetamide & quercetin were purchased from (Sigma- Aldrich, St Louis, MO, USA)

Experimental procedures:

At the end of the experimental period, all rats were fasted overnight, weighed and anaesthetized with intraperitoneal thiopental sodium (40 mg/Kg b.w.). Height (from the tip of the nose to the anus) was measured to calculate body mass index (BMI). A midline abdominal incision was made, the abdominal aorta was exposed and blood samples were collected in plastic tubes, centrifuged at 4000 r.p.m. for 15 minutes for separation of serum and were stored at - 80° till used for determination of the following biochemical measurements:

- 1-Serum aspartate aminotransferase (AST) (Roche Diagnostics, colorimetric method) as described by Moss *et al.* (1987).
- 2-Serum alanine aminotransferase (ALT) (Roche Diagnostics, colorimetric method) as described by Moss *et al.* (1987).
- 3-Serum alkaline phosphatase (ALP) (Roche Diagnostics, colorimetric method as described by Fischbach and Z awta, 1992).
- 4-Serum total bilirubin (Roche Diagnostics, colorimetric method) as described by Sonntag and Scholer, (2001).
- 3-Serum adiponectin (Ani Biotech Oy, using ELISA kit) as described by Hu *et al.* (1996).

The livers were dissected out, washed with sterilized saline, dried between filter papers, weighed, then divided into two parts: one was homogenized and the supernatant was used for measurement of glutathione peroxidase (Bio.diagnostic company, UV method) as described by Paglia and Valentine (1967), catalase (Bio.diagnostic company, colorimetric method) as described by Aebi, (1984) and lipid peroxides (Malondialdehyde, MDA) as described by Draper and Hadley, (1990). The other part of the liver was used for histopathological study.

Histopathological examinations:

The specimens from the right lobe of the liver were taken and fixed immediately in 10% neutral buffered formalin, processed for light microscopy to get (5 μ m) paraffin sections and stained with: Hematoxylin & Eosin to verify histological details and Masson's trichrome staining to demonstrate the collagen fibers as described by *Bancroft and Gamble* (2002).

Statistical Analysis:

All statistical data and significance tests were performed by using SPSS (Statistical Program for Social Science) statistical package (SPSS Inc) version 8.0.1 according to Armitage and Berry (1987). Statistical significance was determined by one-way ANOVA for differences between means of different groups; further analysis was made by LSD (least significance difference) to find intergroupal differences. A probability of P< 0.05 was considered statistically significant. Correlations and Lines of Regression were calculated by linear regression analysis using the Least Square Method. A probability of P < 0.05 was considered statistically significant .All data were expressed as mean ±SEM.

3. Results:

Changes in body weight, body mass index (BMI), liver weight (LW) and liver weight/body weight ratio (LW/BW);

Final body weight and BMI decreased significantly (P < 0.05) in TA group compared to C group, while in TA/Q group, final body weight and BMI were significantly (P < 0.05) increased compared to TA group. Absolute and relative liver weights were significantly (P < 0.05) increased in both TA and TA/Q groups compared to control group (Table 1).

Changes in liver malondialdehyde, Glutathione peroxidase (GPx)and catalase (CAT)

Livers of TA group showed significant (P < 0.05) increase in malondialdehyde as well as significant (P < 0.05) decrease of liver antioxidants (GPx and CAT) compared to C group. On the other hand, TA/Q rats showed significant (P < 0.05) decrease in liver malondialdehyde and significant (P < 0.05) decrease in liver malondialdehyde and significant (P < 0.05) elevation of the liver antioxidants (GPx and CAT) compared to TA rats although liver GPx was still significantly (P < 0.05) lower than C group (Table 2).

Changes in serum adiponectin

Serum adiponectin levels decreased significantly (P < 0.05) in TA rats compared to control rats. In TA/Q rats, significant (P < 0.05) increase in serum adiponectin was observed compared to TA rats, approaching control values (Figure 1)

Changes in liver enzymes (serum ALT, AST and alkaline phosphatase), and serum total bilirubin

TA rats showed significant (P < 0.05) increase in serum liver enzymes (ALT, AST and ALP) as well as total bilirubin compared to C rats. TA/Q rats showed significant (P < 0.05) decrease in serum liver enzymes (ALT, AST and ALP) as well as total bilirubin levels compared to TA rats although values were still significantly (P < 0.05) higher than C group values (Table 3).

Correlations of serum adiponectin versus other parameters in thioacetamide untreated (TA), and thioacetamide / quercetin treated (TA/Q) groups of rats.

TA rats showed significant -ve correlation between serum adiponectin and liver weight/body

weight ratio (P < 0.01), serum liver enzymes (ALT, AST and ALP) (*P*< 0.01, <0.01, <0.05, respectively), total bilirubin (P < 0.01) and liver serum malondialdehyde, (P < 0.01), while the correlations between serum adiponectin and liver antioxidants (GPx and CAT) were significantly +ve(P < 0.01). However, in TA/Q rats the correlations between serum adiponectin and liver weight/body weight ratio, serum liver enzymes (ALT, AST and ALP), serum total bilirubin, liver malondialdehyde as well as liver antioxidants (GPx and CAT) became insignificant (Table 4, Figure 2).

Correlations of liver malondialdhyde versus other parameters in thioacetamide untreated (TA), and thioacetamide / quercetin treated (TA/Q) groups of rats.

TA rats showed significant +ve correlation between liver malondialdehyde and liver weight/body weight ratio (P < 0.01), serum liver enzymes (ALT,AST and ALP) (P < 0.01) and serum total bilirubin (P < 0.01), while the correlations between liver malondialdehyde and liver antioxidants (GPx and CAT) were significantly -ve (P < 0.01). However, in TA/Q rats the correlations between liver malondialdhyde and liver weight/body weight ratio, serum liver enzymes (ALT, AST and ALP), serum total bilirubin , as well as liver antioxidants (GPx and CAT) became insignificant (Table 5, Figure 3).

Histopathological examination of the livers:

Light microscopic examination of the liver of C rats revealed normal architecture of hepatic lobules with hepatocytes radiating from the central veins to the periphery of the lobules (Figures 4 & 5). Livers of TA rats showed disruption of normal architecture of hepatic lobules, in the form of very thick fibrous septa containing numerous fibroblasts in between hepatic lobules, around central veins as well as portal tracts. Central veins were congested with cellular infiltration. Portal tracts were enlarged with dilated branches of portal vein, bile duct proliferation and cellular infiltration. Most hepatocytes had lost most of their cytoplasmic masses and appeared as empty spaces with peripheral cytoplasmic layer, deeply stained nuclei and vacuolations. Blood sinusoids showed congestion and cellular infiltrations rich in fibroblasts (Figures 6, 7, 8). Livers of TA /Q rats showed preservation of nearly normal hepatic architecture. The hepatic lobules appeared with prominent portal areas and congested central veins surrounded with minimal cellular infiltrations (Figures 9, 10).

Table (1): Changes in final body weight (BW, g), boo	ly mass index (BMI, Kg/m2), liver weight (LW, g), liver
weight/ body weight (LW/BW, mg/g) in	control(C), Thioacetamide (TA), and Thioacetamide /
quercetin -treated (TA/Q) groups of rats.	

Groups	BW (g)	BMI (Kg/m2)	LW (g)	LW/BW (mg/g)
C (10)	229.5 ± 3.7	4.9 ± 0.07	4.8 ± 0.20	2.1 ± 0.11
TA (10)	$210.5\pm3.7*$	$4.7 \pm 0.05*$	$7.30\pm0.22*$	$3.5 \pm 0.13*$
TA/Q (10)	221.5 ± 4.6**	$4.8 \pm 0.06*$	$6.8 \pm 0.44*$	$3.0 \pm 0.22*$
Р	< 0.05	< 0.05	< 0.001	< 0.001

P: Significance by 1-way ANOVA among the 3 studied group

*: Significance by LSD at P< 0.05 from control group.

**: Significance by LSD at P< 0.05 from untreated TAA group.

In parenthesis is the number of rats.

Results are expressed as Mean \pm SEM.

Table (2): Liver malondialdhyde (MDA,umol/g tissue), glutathione peroxidase (GPx,mU/mg protein), and
catalase (CAT, U/g tissue) levels in control(C), thioacetamide (TA), and thioacetamide / quercetin-
treated (TA/Q) groups of rats.

Groups	MDA (umol/g)	GPx (<i>mU</i> / <i>mg</i>)	CAT (U/g)
C (10)	2.0 ± 0.25	18.7 ± 0.8	2.1 ± 0.2
TA (10)	$4.8 \pm 0.4*$	$4.9 \pm 0.7*$	$0.6 \pm 0.07*$
TA/Q (10)	2.3 ± 0.3 **	$14.1 \pm 1.4^{*},^{**}$	$1.6 \pm 0.2^{**}$
Р	< 0.001	< 0.001	< 0.001

P:Significance by 1-way ANOVA among the 3 studied groups.

*: Significance by LSD at P< 0.05 from control group.

**: Significance by LSD at P< 0.05 from untreated TAA group.

In parenthesis is the number of rats.

Results are expressed as Mean \pm SEM.



Figure (1); Changes in serum adiponectin (ng/ml) in control(C), thioacetamide (TA), and thioacetamide / quercetin- treated (TA/Q) groups of rats.

*: Significance by LSD at P< 0.05 from control group. **: Significance by LSD at P< 0.05 from untreated TA group

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Table (:	5): Serum	alanı	ne transam	linase (Al	LT, I	U/L), seru	m aspartate ti	ransamı	nase (A	ST, IU/	'L),	total serum
	bilirubin	(T.	bilirubin,	mg/dl),	and	alkaline	phosphatase	(ALP,	IU/L)	levels	in	control(C),
	thioaceta	mide	(TA), and t	hioacetar	nide /	quercetin	-treated (TA/	Q) grou	ps of ra	its.		

		-		
Groups	ALT (IU/L)	AST (IU/L)	T.bilirubin (mg/dl)	ALP (IU/L)
C (10)	27.9 ± 1.5	47.4 ± 2.9	0.23 ± 0.02	203.1 ± 13.1
TA (10)	55.3 ± 1.9*	$88.2 \pm 3.6*$	$0.47 \pm 0.03*$	$404.6 \pm 19.1*$
TA/Q (10)	$43.0 \pm 1.5^{*},^{**}$	66.2 ± 2.2*,**	0.34 ± 0.23 *,**	286.9 ± 18.2*,**
Р	< 0.001	< 0.001	< 0.001	< 0.001

P: Significance by 1-way ANOVA among the 3 studied groups. *: Significance by LSD at P< 0.05 from control group. **: Significance by LSD at P< 0.05 from untreated TAA group. In parenthesis is the number of rats. Results are expressed as Mean \pm SEM.

Table (4): Correlations of serum adiponectin versus liver weiht/body weight (LW/BW), serum alanine transaminase (ALT), serum aspartate transaminase (AST), serum alkaline phosphatase (ALP), total serum bilirubin (T. bilirubin), liver malondialdhyde (L-MDA), glutathione peroxidase (GPx), Catalase (CAT)levels in thioacetamide (TA), and thioacetamide / quercetin- treated (TA/Q) groups of rats.

Groups		Lw/Bw	ALT	AST	ALP	T.bilirubin	L- MDA	GPx	CAT
		(mg/g)	(IU/L)	(IU/L)	(IU/L)	(mg/dl)	(umol/g)	(mU/mg)	(U/g)
TA(10)	r	-0.683	-0.605	-0.505	-0.566	-0.580	-0.648	0.548	0.755
	Р	< 0.01	< 0.01	< 0.05	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
TA/Q(10)	r	-0.185	0.206	-0.77	110	-0.97	-0.279	-0.161	0.346
	Р	NS	NS	NS	NS	NS	NS	NS	NS

In parenthesis is the number of rats.

NS: not significant.



Figure (2): showing correlations of serum adiponectin (ng/ml) versus liver weight/ body weight ratio, liver malondialdehyde, serum alanine transaminase and liver glutathione peroxidase (P < 0.01) in thioacetamide (TA) rats.

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Table (5): Correlations of Liver malondialdehyde (L-MDA) versus liver weight/body weight (LW/BW), serum
alanine transaminase (ALT), serum aspartate transaminase (AST), serum alkaline phosphatase
(ALP), total serum bilirubin (T.bilirubin), glutathione peroxidase(GPx), Catalase (CAT)levels in
thioacetamide (TA), and thioacetamide / quercetin treated (TA/Q) groups of rats.

tinoactiannuc (TA), and tinoactiannuc / queretin treated (TA/Q) groups of rats.									
Groups		Lw/Bw	ALT	AST	ALP	T.bilirubin	GPx	CAT	
		(mg/g)	(IU/L)	(IU/L)	(IU/L)	(mg/dl)	(mU/mg)	(U/g)	
TA(10)	r	0.860	0.690	0.635	0.860	0.688	-0.748	-0.825	
	Р	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	
TA/Q(10)	r	0.420	-0.107	-0.028	-0.219	-0.033	0.333	-0.187	
	Р	NS	NS	NS	NS	NS	NS	NS	

In parenthesis is the number of rats.

NS: not significant.



Figure (3): showing correlations of liver malondialdehyde versus liver weight/ body weight ratio, serum alanine transaminase and liver glutathione peroxidase (P< 0.01) in thioacetamide (TA) rats.



group showing normal hepatic lobule (Hx & E, 100 X).



Fig. 5: A photomicrograph of section of liver of control group showing hepatocytes with acidophilic cytoplasm and central vesicular nuclei (Hx & E, 400 X).



Fig. 6: A photomicrograph of section of liver of TA group showing loss in the normal architecture of the hepatic lobules. (Hx & E, 100 X).



Fig. 7: A photomicrograph of section of liver of TA group showing very thick septa around congested central veins, cellular infiltration and congested blood sinusoid. (Hx & E, 400 X).



Fig. 8: A photomicrograph of section of liver of TA group showing very thick septa around portal tract, congested portal vein and hepatic artery. (Masson's trichrome, 400 X)



showing preservation of nearly normal hepatic architecture. Notice congested portal vein. (Hx & E, 100 X).

4. Discussion

In the present study, rats exposed to liver damage by thioacetamide showed significant weight loss possibly due to enhanced lipolysis as evidenced by the significant decrease in BMI in addition to decreased appetite as a result of increased 5-HT as previously reported by Haider et al. (2004). Liver weight increased significantly in TA rats which agree



group showing fibrous septa around central vein and in between hepatic lobules. (Masson's trichrome, 100X).

with the findings of Jeon et al. (2003) and Amalia et al. (2007) and could be explained by the inflammatory changes seen in the liver in the form of vascular congestion, infiltration by leukocytes, and fibrosis. Hepatocellular damage was also evident by the biochemical study in the form of elevated serum levels f liver enzymes and total bilirubin, a picture reported by many authors with different hepatotoxic

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agents that eventually lead to liver fibrosis or cirrhosis (Badr et al., 2009 and Jayaraman et al., 2009).In the present study, liver peroxides increased significantly and a significant +ve correlation was established between liver peroxides and relative liver weight as well as liver enzymes in TA rats suggesting that liver peroxides contributed to thioacetamide induced liver structural and functional changes. Nevertheless, their contribution to the onset of liver injury by thioacetamide is debatable. Thioacetamide was reported to induce liver trauma by interfering with protein synthesis and enzyme metabolism (Liu et al., 2010). Increased lipid peroxides were reported to occur two weeks after the onset of liver necrosis and cholestasis in the bile duct ligation -model of liver cirrhosis (Parola et al., 1996). In the present study, the significant increase in liver peroxides in TA rats could be the consequence of fatty acid accumulation, a condition known as steatosis which was reported by Adenolfi et al. (2001) to be the first hit that increases liver sensitivity to a second hit by oxidative stress or inflammation in the pathogenesis of non alcoholic hepatosteatotitis (NASH) and insulin resistance was claimed to be a contributing factor to steatosis (Chitturi et al., 2001). The severity of steatosis was found to correlate with the extent of hepatic stellate cell (HSC) activation which is the liver cell responsible for deposition of extracellular matrix proteins and consequently fibrosis (Cortez et al .,2001). In the present study, the cause of fatty acid accumulation in the livers of TA rats was difficult to speculate, but it could be due to decreased fatty acid oxidation by hepatocytes due to cellular injury as reported by Liu et el. (2010) as well as decreased hepatocyte sensitivity to insulin due to decreased circulating adiponectin level. Lipid peroxides were reported to induce alterations in cell membrane structure due to induction of (CYP)2E, the primary enzyme involved in bioactivation of thioacetamide to thioacetamide sulfoxide and thioacetamide sulfdioxide which are reactive metabolites that would induce damage of cellular membrane and organelles (Wang et al., 2000 and Jaeschke et al., 2011). Lipid peroxides were found to trigger a series of cytotoxic reactions either directly by interacting with biological macromolecules like proteins and DNA leading eventually to cell death (Czeczot et al., 2010) or indirectly by eliciting an autoimmune reaction as reported by Vidali et al. (2008). In addition to lipid peroxides, increased oxidative stress could result from activated neutrophils, macrophages and monocytes which were reported to release various malicious prooxidants that might contribute to cellular damage (Lochner et al., 2009). The significant decrease of liver antioxidants in TA rats might be the result of increased

consumption in defense against free radicals as evidenced by the -ve correlation between liver peroxides and liver antioxidants or decreased synthesis by the already injured or damaged hepatocytes or both which would establish a vicious circle in which oxidative stress depletes antioxidant defense with more liver susceptibility to oxidative damage. Administering an antioxidant might have the rationale of interrupting this vicious circle and conferring hepatoprotection. Various antioxidants (Vitamin A, E, C, selenium and Beta carotene) have been tried in liver cirrhosis but the results were conflicting; some authors were with (Mehmetçik et al., 2008 and Passoni and Coelho, 2008) and the others were against (Bjelakovic et al., 2011). However, until now no therapy has proved radical cure.

Fruits, vegetables, spices, and tea provide essential nutrients and many diet-derived phenolics, in particular flavonoids, which have been reported to exert potential anticarcinogenic activities (Middleton et al., 2000 and Surh, 2003). Quercetin is one of the most common flavonoids found in the diet (Yang et al., 2001). In the present study, rats treated with quercetin 3 weeks after induction of hepatotoxicity showed signs of improvement by histological and biochemical studies. We may suggest that quercetin might have potentiated the antioxidant defense in the liver, thus interrupting the vicious circle between oxidative stress and oxidative damage as shown by the significant decrease of liver peroxides and increase of its antioxidants. Quercetin was found to be involved in modulation of enzymes involved in proliferation and signal transduction pathways including members of the MAPK family and Akt (Yoshizumi et al., 2001and Spencer et al., 2003) as well as inhibition of PI-3-kinase (Agullo et al., 1997).

It was of interest to observe that serum adiponectin level decreased significantly in TA rats which agree with the findings of Latif et al. (2010) and disagree with the findings of Salman et al. (2010) who reported increased adiponectin level in patients with liver cirrhosis. In the present study, serum adiponectin correlated significantly and negatively with relative liver weight, liver peroxides, serum liver enzymes and bilirubin which further confirm the hepatoprotective role of adiponectin, a finding previously reported by Masaki et al.(2004) who found that alcohol -induced steatohepatitis was partially mediated by adiponectin deficiency and was ameliorated by adiponectin administration via induction of hepatic fatty acid oxidation and inhibition of fatty acid synthesis. Adiponectin exerts hepatoprotection via inhibition of steatogenesis and fibrogenesis at multiple levels (Xu et al., 2003). These levels involve attenuation of oxidative stress and proinflammatory cytokine

production. Adiponectin attenuates the effect of TNF- β 1 on the expression of fibrogenic genes such as connective tissue growth factor (Kamada et al., 2003 and Antoniades et al, 2009), modulation of inflammatory responses in endothelial cells by inhibiting NF-KB ,TNF- α release and TNF- α mRNA expression (Ouchi et al., 2000 and Masaki et al., 2004), suppression of macrophage function (Tsatsanis et al., 2005), modulation of the activated phenotype of HSC, which express both adiponectin receptors (Ding et al., 2005and Caligiuri et al., 2008). Suppression of proliferation and migration of mouse HSC stimulated with platelet derived growth factor (PDGF) -BB, one of the most potent mitogens and chemotactic factors for HSC (Kamada et al., 2003). Two adiponectin receptors have been identified (Adipo R1/R2) and were reported to be responsible for the effect of adiponectin on PPARa expression and AMPK activation at the hepatic level (Kadowaki & Yamauchi, 2005). It was difficult to speculate whether adiponectin deficiency in TA rats was the cause or the consequence of thioacetamide -induced hepatotoxicity but the observation that adiponectin level was restored almost to normal value by quercetin in TA/Q suggest that oxidative stress was implicated -at least partially in adiponectin deficiency. It could be possible that lipid peroxides and inflammatory mediators that had triggered hepatic damage also decreased adiponectin production by adipocytes which in turn contributed to hepatic damage as previously reported by Lago et al. (2007) who found that adiponectin expression was down regulated in the presence of inflammation. Elevated adiponectin level in TA/Q rats by quercetin therapy might have teamed up with the attenuated oxidative stress to confer more hepatoprotection.

In conclusion, increased oxidative stress was implicated in thioacetamide –induced liver cirrhosis and administration of quercetin after onset of hepatic injury by thioacatamide was effective in slowing down the progress of cirrhotic and hepatic functional derangements. Whether an earlier administration of quercetin or the use of a higher dosage could produce better outcome is a matter of speculation that needs further research.

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