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Hepatoprotective effect of ginger and grape seed, alone and in combination orally, in paracetamol induced acute liver toxicity in rats

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Liver toxicity due to overdoses of common medicines is not uncommon. Paracetomol (acetaminophen) is one of the most common medicines prescribed by physicians and its overdose is toxic to liver. Here, we investigated the hepatoprotective effects of ginger and grape seed alone and/or in combination against paracetamol induced liver toxicity in rats as the ginger may potentiate the effect of grape seed. Fifty-Six male albino rats were divided into seven groups: group (I) normal control, (II) positive control, (III & V) rats treated with ginger extract, (IV & VI) rats treated with grape seed extract and (VII) rats treated with ginger extract and grape seed extract in combination. All extracts were administered orally for 28 days. On day 29, groups II, V, VI and VII were orally administrated a single dose of paracetamol (2 g/kg) which resulted into a significant increase in plasma liver enzymes, TNF-α, NO and TBARS, and also a significant decrease in liver antioxidants as well as plasma HDL. Our results showed that the ginger and grape seed alone may be effective in the protection of liver toxicity. However, prominent effect was found in the combined treatment through radical scavenging effect and antioxidant activity which is confirmed by histopathological examination of the liver.

Keywords: Acetaminophen, 4'-Hydroxyacetanilide, Oxidative stress biomarkers, Proanthocyanidin extract, *Vitis* sp., *Zingiber officinale*

The liver, being the center of metabolic functions, plays a crucial role in metabolizing a variety of xenobiotics, and hence, more vulnerable to the toxicity of these chemicals. Overdoses of acetaminophen (paracetamol) represent one of the most common pharmaceutical product poisonings in humans today. Although it is considered safe at therapeutic doses, yet in overdose, acetaminophen produces hepatic necrosis that can be fatal. Whereas the initial biochemical and metabolic events that occur in the early stages of toxicity have been well described, the precise mechanisms of hepatocyte death are poorly understood[1]. Normally, paracetamol is metabolized by cytochrome P450 enzymes into an active intermediate; N-acetyl-p-benzoquinone imine (NAPQI), which is rapidly detoxified by conjugation with glutathione. Excess NAPQI binds to the mitochondrial proteins and damages the mitochondria in hepatocytes, leading to generation of free radicals followed by lipid peroxidation and finally hepatic cell death[2].

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Many studies have shown that natural antioxidants obtained from different alternative systems of medicine display a wide range of biological activities in order to minimize paracetamol induced oxidative stress in animal models[3]. Ginger belongs to a tropical and sub-tropical family Zingiberaceae, and it has been cultivated for thousands of years as a spice and for medicinal purposes. For centuries, it has been used for the treatment of rheumatism, gingivitis, toothache, asthma, stroke, nausea, vomiting and diabetes[4,5]. Extracts of the ginger are rich in shagaols and gingerols which exhibit anti-inflammatory, antioxidant, anticarcinogenic and antinociceptive properties under *in vitro* and *in vivo* systems and also beneficial effects on CNS activity[6-8].

Ginger shows a hepatoprotective effect in the pretreatment in acute liver toxicity induced by acetaminophen through assessing the liver enzymes and some of the oxidative stress biomarkers[9].

Grape seed proanthocyanidin extract (GSPE), an extract from red grape seeds containing a variety of phenolic compounds, is widely marketed as a dietary supplement with a variety of health benefits. The most abundant phenolic compounds isolated from grape seed are flavan-3-ols (catechins) including catechin,

epicatechin, epicatechin gallate, procyanidin dimers (the most common is procyanidin B2), trimers and more highly polymerized procyanidins (often referred to as oligomeric proanthocyanidins or condensed tannins). GSPEs are powerful free radical scavengers, being more effective than either ascorbic acid, vitamin E or β- carotene[10]. Singha & Das[11] have reported that the grape extract pretreatment, particularly the seed extract compared to that of skin and pulp, significantly ameliorated the ionizing radiation-induced alterations in human erythrocytes *in vitro*. In another experiment on scavenging and antioxidant properties of grape seed extract on IR-induced liver damage, they observed that it could serve as a potential source of natural antioxidant against lower doses of IR-induced oxidative stress[12].

In the present study, we evaluated possible hepatoprotective effect of both ginger and grape seed in paracetamol induced liver toxicity rat model. In addition, we investigated the possible mechanism of action of both of them and examine its histopathological effect.

Material and Methods

Animals

Fifty-Six male albino rats, weighting 190±10 g, 6-7 weeks of age, at the start of the experiments were purchased from Faculty of Veterinary Medicine, Cairo University. Prior to the initiation of the study, the animals were randomized and assigned to treatment groups. Four rats were housed per cage (26×41 cm) and placed in the experimental room for acclimatization 24 h before the test. The animals were fed with standard laboratory diet and with tap water *ad libitum*, and kept in an air-conditioned animal room at 23±1°C with a 12 h light/dark cycle. Animal care and handling was performed in conformance with approved protocols of Cairo University and Egyptian Community guidelines for animal care.

Experimental groups, treatment samples and induction of hepatotoxicity

Paracetamol 500 mg/tablet (El-Nile Pharmaceutical Company, Egypt), Ginger 400 mg/tablet and Grape seed 150 mg/capsule (Mepaco-Pharma, Egypt) were purchased, dissolved in 0.9% saline and administered orally. Heaptotoxicity was induced by administration of paracetamol in a single dose of 2 g/kg[13].

Experimental

Rats were randomly allocated into seven groups of eight animals each as follows: Gr. I: Normal control group and Gr. II: Positive control had similar volume of 0.9% saline orally) for 28 days. Gr. III & V had ginger extract (400 mg/kg) suspended in 0.9% saline orally in a single daily dose for 28 days[14] while Gr. IV & VI had grape seed extract (400 mg/kg) suspended in 0.9% saline orally in a single daily dose for 28 days[15]. Gr. VII had both ginger extract and grape seed extract (400 mg/kg each) suspended in 0.9% saline orally in a single daily dose for 28 days. On day 29, all animals in groups II, V, VI and VII were orally administrated a single dose of paracetamol (2 g/kg).

Blood, liver samples and biochemical analysis:

Preparation of blood samples

On day 30, rats were fasted overnight, anesthetized with thiopental sodium (50 mg/kg) and blood samples were collected (5 mL per rat) into heparinized tubes. The heparinized blood samples were centrifuged at 1000×g for 20 min. The separated plasma was used for estimation of plasma activity of alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH) as well as levels of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C)[16].

Preparation of liver samples

Animals were euthanized by cervical dislocation, and then liver was rapidly removed from each rat. A part of each liver was fixed in formalin-saline for 48 h for histopathological study. The other part of each liver was weighed and homogenized, using glass homogenizer (Universal Lab. Aid MPW-309, mechanika precyzyjna, Poland), with ice-cooled saline to prepare 25% W/V homogenate. The homogenate was divided into three aliquots as follows: The first one was deproteinized with ice-cooled 12% trichloroacetic acid and the obtained supernatant, after centrifugation at 1000×g, was used for the estimation of reduced glutathione (GSH).

The second aliquot was centrifuged at 1000×g and the resultant supernatant was used for estimation of thiobarbituric acid reactive substances (TBARS), tumor necrosis factor-α (TNF-α), nitric oxide (NO) and total protein.

The third aliquot of homogenate was used to prepare a cytosolic fraction of the liver by centrifugation at 10500×g for 15 min at 4□ using a cooling ultra-centrifuge (Sorvall comiplus T-880, Du Pont, USA), and the clear supernatant (cytosolic

fraction) was used for determination of succinate dehydrogenase (SDH), glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT) activities[16].

Biochemical analysis

Analysis of plasma was carried out for transaminases (L-alanine and L-aspartate) using colorimetric method (TECO DIAGNOSTICS, USA), LDH activity using colorimetric assay kit (BioVision Inc, USA) and TBARS level using Cayman Chemical assay kit, USA, Liver TNF-α was measured using rat ELISA kit, Sigma Aldrich, USA and NO was determined using colorimetric assay kit (BioVision Inc, USA). CAT and SOD were determined using Abnova assay kit, USA, SDH using colorimetric assay kit (BioVision Inc, USA), GPx and GSH levels using Cayman Chemical assay kit, USA,

Plasma TG was determined using enzymatic assay kit (XpressBio life science products, USA), TC, HDL-C and LDL-C were estimated using colorimetric method using (Biochain, USA). The protein content of liver tissue was measured following Lowry *et al.*[17].

Histopathological examination

The liver tissues isolated from the test animals were fixed in formalin-saline for 48 h. The fixed tissue was processed manually through graded ethanol, cleared in xylene, impregnated and embedded in paraffin wax. Thin sections were cut with a rotary microtome, stained by haematoxylin and eosin technique, examined microscopically for pathological changes according to the method of Bancroft and Steven.

Statistical analysis

All data were expressed as mean ± SD and analyzed using SPSS program version 15. For all parameters, comparisons among groups were carried out using one-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparisons test. All P values reported are two-tailed and $P < 0.05$ was considered significance.

Results

Effect of ginger and grape seed extracts on blood liver enzymes (ALT, AST and LDH)

Mean plasma level of ALT, AST and LDH were significantly increased in positive group compared to the control group ($P < 0.01$). On the other hand, the mean plasma level of liver enzymes were significantly decreased in groups receiving ginger and grape seed extracts (400 mg/kg) when compared to positive control group ($P < 0.01$). The combination of ginger and grape seed at dose 400 mg/kg resulted in decreased ALT, AST and LDH levels compared to the positive control group ($P < 0.01$). The effect of ginger extract was pronounced than the grape seed extract (Table 1).

Effect of ginger and grape seed extracts on plasma lipid profile

Table 1 showed that oral administration of paracetamol at 2 g/kg resulted in a significant increase in plasma total cholesterol (TC), triglycerides (TG) and LDL-C compared with the normal control group ($P < 0.01$). Supplementation of ginger and grape seed extracts resulted in a significant decrease in plasma TC, TG and LDL-C as compared with the positive control group ($P < 0.05$). Also, oral administration of paracetamol resulted in a significant decrease in plasma HDL-C compared to the normal control group ($P < 0.01$). Supplementation of ginger and grape seed extracts resulted in a significant increase in plasma HDL-C as compared with the group that received paracetamol ($P < 0.01$).

Table 1 — The effect of ginger and grape seed extracts on activity of plasma alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH) and lipid profile in all experimental groups of rats

Groups	ALT (U/L)	AST (U/L)	LDH (U/L)	TC (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)
I. Normal	17.4±3.05	12.6±2.44	119±7.58	155±8.09	99.2±8.47	58.4±6.18	76.8±7.09
II. Positive control Paracetamol (2 g/kg)	82.7±6.52^{a}	47.6±6.38^{a}	231±9.84^{a}	208±16.1^{a}	142±9.73^{a}	40.6±4.87^{a}	138±8.73^{a}
III. Ginger extract(400 mg/kg)	17.6±1.88^{b}	11.8±2.5^{b}	118±5.48^{b}	169±9.93^{ab}	104±11.8^{b}	52.9±4.62^{b}	95.8±6.40^{b}
IV. Grape seed extract (400 mg/kg body wt.)	16.5±3.32^{b}	23.5±4.8^{abc}	116±8.67^{b}	159±9.7^{b}	97.5±10.7^{b}	50.9±4.27^{b}	92.2±6.38^{ab}
V. Ginger + Paracetamol	20.2±3.38^{b}	12.5±2.75^{bd}	123±6.18^{b}	163±7.25^{b}	105±11.3^{b}	53.1±6.02^{b}	92.6±8.74^{ab}
VI. Grape seed+ Paracetamol	27.1±2.79^{ab}	16.2±3.6^{abd}	145±5.94^{abde}	175±17.5^{abe}	118±8.5^{bcde}	43.3±4.96^{a}	108±8.11^{abde}
VII. Ginger + Grape seed + Paracetamol	19.6±2.12^{b}	12.9±2.65^{bd}	121±5.48^{bf}	158±8.68^{bcf}	105±6.47^{bf}	54.05±5.22^{b}	83.3±6.56^{bf}

[Ginger and Grape seed were orally given daily for 28 days. Paracetamol was given orally as a single daily dose of 2 g/kg, at day 29. Blood samples were collected 24 h after paracetamol administration. Results are expressed as mean ± SD. a: significant from normal control; b: significant from positive control; c: significant from Ginger group; d: significant from grape seed group; e: significant from Ginger + Paracetamol group; and f: significant from Grape seed + Paracetamol group. Values are statistically significant at *$P < 0.05$]

Effect of ginger and grape seed extracts on liver TNF-α, NO, TBARS GSH and total protein

Table 2 showed that oral administration of paracetamol at 2 g/kg resulted in a significant increase in plasma tumor necrosis factor-α (TNF-α), nitric oxide (NO) and thiobarbaturic acid reactive substances (TBARS) compared to the normal control group (P<0.01). Rat receiving any of the two extracts of ginger or grape seed or in combination used in this study (400 mg/kg) showed a significant decrease in plasma TNF-α, NO and TBARS compared to the group that received paracetamol (P <0.01). Furthermore, the results of the present study showed that oral administration of paracetamol at 2 g/kg resulted in a significant decrease in liver reduced glutathione (GSH) and total protein compared to the normal control group (P <0.01). Rat receiving extract of any of the two extracts of ginger and grape seed in this study (400 mg/kg) showed a significant increase in liver reduced glutathione (GSH) and total protein compared with the group that received paracetamol (P <0.01). The effect of ginger extract was pronounced more than grape seed extract.

Effect of ginger and grape seed extract on liver SOD, CAT, SDH and GPx

Table 3 showed that oral administration of paracetamol at 2 g/kg resulted in a significant decrease in the liver activities of superoxide dismutase (SOD), catalase (CAT), succinate dehydrogenase (SDH) and glutathione peroxidase (GPx) compared to the normal control group (P <0.01). Rat receiving extract of any of the two extracts of ginger or grape seed or in combination used in this study showed a significant increase in liver SOD, CAT, SDH and GPx compared to the paracetamol group (P <0.01).

Histopathological changes associated with prophylactic effects of ginger and grape seed extract against paracetamol induced hepatotoxicity.

Sections from the control group (C) showed normal histological appearance as they showed preserved integrity of the liver surface, normal orientation and distribution of hepatocytes. The paracetamol group showed histological features of spotty liver necrosis with dense neutrophilic infiltrate. Group III & IV look to be within normal appearance, group V showed

Table 2 — The effect of ginger and grape seed extracts on level of liver tumor necrosis factor-α (TNF-α), nitric oxide (NO), thiobarbaturic acid reactive substances (TBARS), total protein and reduced glutathione (GSH) in all experimental groups of rats

Groups	TNF-α (Pg/mg protein)	NO (ug/mg protein)	TBARS (nmol/mg protein)	Protein (mg/g tissue)	GSH (umol/mg protein)
I. Normal	19.6±2.73	83.9±8.14	71.4±5.89	101±4.61	15.9±2.80
II. Positive control Paracetamol (2 g/kg)	94.3±5.61^{a}	138±12.1^{a}	143±7.61^{a}	68.5±5.03^{a}	4.27±0.96^{a}
III. Ginger extract(400 mg/kg)	19.1±3.80^{b}	81.3±5.71^{b}	69.6±5.48^{b}	97.7±5.35^{b}	15.6±1.21^{b}
IV. Grape seed extract (400 mg/kg body wt.)	18.7±2.65^{b}	82.8±4.94^{b}	69.9±4.12^{b}	101±8.17^{b}	16.7±1.64^{b}
V. Ginger + Paracetamol	23.5±3.74^{b}	89.5±7.02^{b}	81.8±8.10^{ab}	89.2±5.76^{ab}	13.9±1.42^{b}
VI. Grape seed+ Paracetamol	33.2±3.93^{abcde}	105.5±5.29^{ab}	96.7±5.77^{ab}	77.4±6.40^{abcde}	9.52±2.22^{abcd}
VII. Ginger + Grape seed + Paracetamol	25.7±2.64^{bf}	86.4±6.90^{abf}	79.8±3.37^{bcdf}	103±8.09^{bef}	16.7±1.56^{bf}

[Ginger and Grape seed were orally given daily 28 days. Paracetamol was given orally as a single daily dose of 2 g/kg, at day 29. Blood samples were collected 24 h after paracetamol administration. Values are given as mean ± SD for groups of eight animals each. a: significant from normal control; b: significant from positive control; c: significant from Ginger group; d: significant from grape seed group; e: significant from Ginger + Paracetamol group; and f: significant from Grape seed + Paracetamol group. Values are statistically significant at *P <0.05]

Table 3 — The effect of ginger and grape seed extracts on level of liver succinate dehydrogenase (SDH), superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activities in all experimental groups of rats

Groups	SDH (umol substrate transformed/mg protein/min)	SOD (U/mg protein)	CAT (H2O decomposed/ min/mg protein)	GPx (U/mg protein)
I. Normal	115.56±6.33	9.28±1.81	71.2±4.19	13.3±1.76
II. Positive control Paracetamol (2 g/kg)	83.3±9.89^{a}	3.92±0.49^{a}	38.6±3.60^{a}	6.55±1.19^{a}
III. Ginger extract(400 mg/kg)	119±13.5^{b}	9.80±0.72^{b}	72.7±5.11^{b}	13.2±1.49^{b}
IV. Grape seed extract (400 mg/kg body wt.)	106±5.60^{b}	9.04±1.18^{b}	79.8±6.04^{b}	13.2±1.82^{b}
V. Ginger + Paracetamol	109±10.3^{b}	8.18±1.31^{b}	66.9±6.43^{b}	11.5±1.24^{b}
VI. Grape seed+ Paracetamol	98.1±6.83^{b}	6.72±1.35^{abcd}	59.8±4.27^{abcd}	8.80±1.68^{abcde}
VII. Ginger + Grape seed + Paracetamol	115±13.1^{b}	9.16±0.85^{b}	73.1±3.23^{b}	13.6±1.91^{bf}

[Ginger and Grape were orally given daily for 28 days. Paracetamol was given orally as a single daily dose of 2 g/kg, at day 29. Blood samples were collected 24 h after paracetamol administration. Values are given as mean ± SD for groups of eight animals each. a: significant from normal control; b: significant from positive control; c: significant from Ginger group; d: significant from grape seed group; e: significant from Ginger + Paracetamol group; and f: significant from Grape seed + Paracetamol group. Values are statistically significant at *P <0.05]

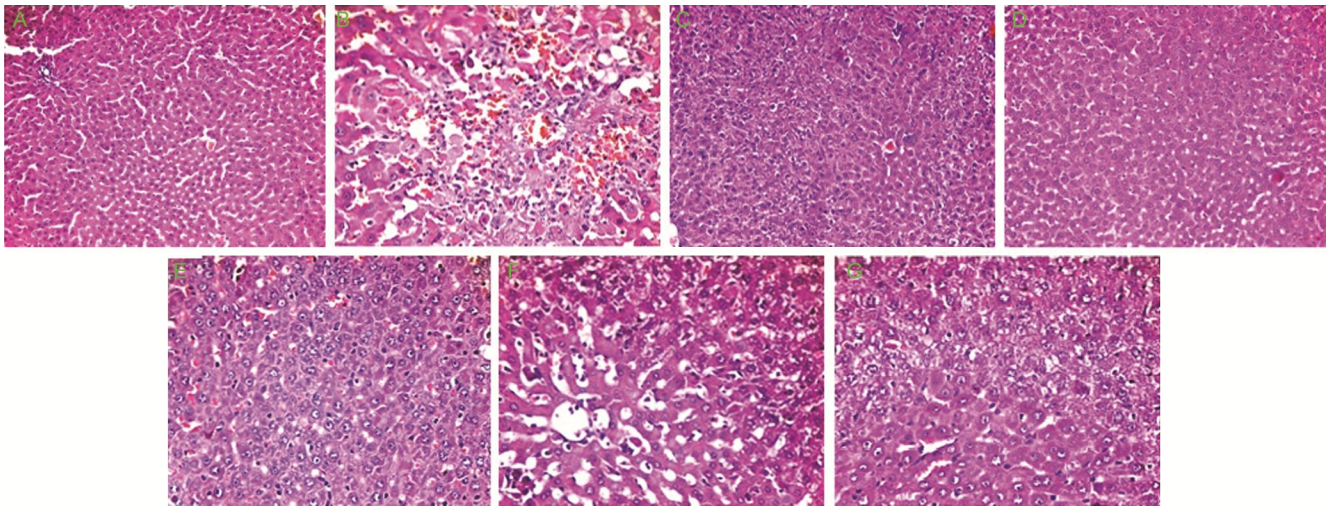

Fig. 1 — Histopathological sections of hematoxylin and Eosin (H and E) stained rat liver of the following treated groups: (A) Control with intact superficial layer, normal population and orientation of hepatocytes. (B) Paracetamol with spotty liver necrosis, dense neutrophilic infiltrate and sinusoidal congestion. (C) Ginger 400 mg/kg with liver histology looks to be within normal appearance, (D) Grape seed 400 mg/kg with liver histology looks to be within normal appearance. (E) Ginger 400 mg/kg + paracetamol with reparative liver cells, inflammation subsides with improvement of neutrophilic infiltrate. (F) Grape seed 400 mg/kg + paracetamol with less inflammation and wide hydrophobic degenration. (G) Ginger 400 mg/kg + grape seed 400 mg/kg + paracetamol with minimal hydrophobic degeneration and minimal inflammation. [Magnification for A, C and D was 200X and B, E, F and G was 400X]

improvement of neutrophilic infiltrate, group VI appeared with less inflammation and wide hydrophobic degeneration and group VII showed minimal hydrophobic degeneration and inflammation as seen in Fig. 1.

Discussion

Paracetamol (4'-hydroxyacetanilide) is oral analgesic and antipyretic drug. It is metabolized extensively by the liver *via* three main pathways; sulfonation, glucuronidation and oxidation . The first two pathways are quantitatively more important than the last one, but the oxidative pathway is the culprit as far as toxicity is concerned[18]. Oxidation of paracetamol occurs in the hepatic microsomes and is primarily catalyzed by cytochrome P-450[19]. The process produces a highly reactive arylating compound called N-acetyl-p-benzoquinoneimine (NAPQI). When more NAPQI are formed with a rate greater than its conjugation to GSH, the unbound NAPQI becomes toxic by binding to macromolecules, including cellular proteins[20].

Medicinal plant based medicines are potential sources of naturally occurring phytoconstituents that may act in a variety of ways to suppress the generation of reactive oxygen species. These phytoconstituents have broad ranges of pharmacological activities[21,22]. In the present study administration of paracetamol treated rats showed an increase in the activities of AST, ALT, LDH and TBARs levels, on the other hand, it showed a decrease of liver total protein levels besides GSH, SDH, SOD, CAT and GPx activities when compared with control rats. Oral administration of ginger and grape seed extract and paracetamol treated rats showed an inhibition in elevation of plasma AST, ALT and LDH and in elevation of liver total protein, GSH, SDH, SOD, GPx and CAT levels compared to paracetamol treated rats. Long *et al*.[23] have reported that administration of grape seed extract significantly reduced plasma AST and ALT activities and also decreased hepatic MDA and increased antioxidants levels.

Phytochemical studies have shown that the medicinal properties of ginger are due to the presence of phytochemicals such as zingerone, shogaols, gingerols, pardols, β-phellandrene, curcumene, cineole, geranyl acetate, terphineol, terpenes, zingiberol, linalool, α-zingiberene, zingiberenol and α-farmesene[24-26].

Administering ginger extract mitigated the oxidative stress by increasing the activity of antioxidant enzymes activities and decreasing the levels of lipid peroxidation in the rat liver and significantly reduced AFB1 induced toxicity on the serum marker of liver damage[27]. In addition to the extract, studies have also shown that feeding rats a diet containing ginger was also effective against the CCl_4-induced liver damage

where the levels of serum AST, ALT, ALP and lipid peroxidation was decreased[28].

Studies have shown that coadministration of the aqueous extract of ginger (3 mg/animal/day), along with paraben for 30 days ameliorated the toxin-induced lipid peroxidation[29]. Administering ginger increases the activities of SOD, GPx, CAT and the non enzymatic antioxidants (GSH and ascorbic acid) in the mouse liver, and therefore reduces the toxic effects of parabens[30].

Molecular studies have also shown that ginger reduces the elevated expression of NFκB and TNF-α in liver cancer rats, suggesting that the observed chemopreventive effects may be mediated through the inhibitory effects on NFκB, possibly through the suppression of the proinflammatory TNF-α[30].

Furthermore, grape seed have been widely studied because of their antioxidant properties. It is well described in the literature that ginger and grape seed can afford protection against neurodegenerative and metabolic diseases[8,31,32]. In addition, some studies have also demonstrated the benefits of compounds present in grapes to the liver. The hydroalcoholic extract of black grapes was found to prevent lead-induced oxidative stress[33].

The present study demonstrated that pretreatment with grape seed extract significantly ameliorated the lipid peroxidation induced by acetaminophen as manifested by the decreased MDA level, accompanied by the increased GSH content and enhanced activities of CAT and SOD. These results could be attributed to the potential antioxidant effects of grape seed extract. In addition, grape seed extract normalized the elevation of TNF-α production after acetaminophen toxicity. Additionally, grape seed extract has also remarkably reduced production of NO approaching the control levels. These findings might be useful for attributing the anti-inflammatory effect and are in agreement with those obtained by earlier researchers[34-36] .

Lipids are the most important cellular entities which are not only the constituents of cell membrane but also involved in many cellular, metabolic functions and energy production. The changes in plasma lipids level could be sensitive and serve as a simple marker for assessing liver disorders. In the present study, administration of paracetamol treated rats showed an increase in the cholesterol level when compared with control rats. Ginger has significantly reduced the serum total cholesterol and triglycerides and increased the HDL in pathogenic diabetic rats[37]. It has been suggested that the aqueous extract of ginger might inhibit the intestinal absorption of dietary fat by inhibiting its hydrolysis[37]. The ginger has showed hypolipidemic effect. Ginger acts as a hypolipidemic agent in cholesterol-fed rabbits and reported that an ethanolic extract of ginger prevents hypercholesterolemia and development of atherosclerosis in cholesterol-fed rabbits[38].

The hyperlipidemic mice receiving alcohol-free red wine obtained a reduction in total and LDL cholesterol as compared with controls. The hyperlipidemic effect of polyphenols in red wine has been associated with the fact that these compounds can bind to cholesterol, blocking its absorption. In this situation, the fecal excretion of cholesterol, bile acids, and other dietary lipids are increased[39].

Our study showed that the treatment of rats with ginger or grape seed extract alone or in combination normalized the levels of cholesterol, triglycerides and HDL. This may be due to that ginger inhibits hepatic fatty acid synthesis by lowering the key enzymes activities in supplying substrates, thus reducing cholesterol, HDL and triglyceride levels in serum. It was confirmed that the hypocholesterolemic effect of ginger could have possibly resulted from the inhibition of cellular cholesterol biosynthesis after the consumption of the ginger extract[40]. Ginger and grape seed extracts were found to have hypocholesterolemic effects and hence decrease plasma total cholesterol and plasma alkaline phosphatase in adult male rats[41].

Conclusion

The ginger and grape seed extracts had hepatoprotective effect in liver toxicity model in rats. This hepatoprotective effects is probably exerted via anti-inflammatory and antioxidant effect as it significantly reduced level of TNF-α, nitric oxide and thiobarbaturic acid reactive substances, after 28 days of prophylactic treatment in liver toxicity rats. Ginger and grape seed also improved oxidative stress levels. Further pharmacological and clinical studies are needed to evaluate this effect as well as its potential use in treatment of liver toxicity in human.

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