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Research Article

Therapeutic Implication of Honey against Chronic Carbon Tetrachloride-Induced Liver Injury *via* Enhancing Antioxidant Potential and Maintenance of Liver Tissue Architecture

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ABSTRACT

The current study was undertaken to examine the possible hepatoprotective effect of natural honey against carbon tetrachloride (CCl_4)-induced liver injury in mice. A significant increase in the serum aminotransferases (ALT and AST) and alkaline phosphatase activity was noticed in mice exposed to CCl_4. In addition to this, a significant decrease in total antioxidant capacity and antioxidant enzymes (catalase, glutathione peroxidase and superoxide dismutase) was observed in CCl_4-induction group. However, treatment with honey (400 mg/kg b.w, 4 times/ week) clearly demonstrates significant hepatoprotective activities by lowering the liver marker enzymes towards the normal reference range and restores the antioxidant enzyme levels($p<0.05$). The effect of CCl_4 was also noticed microscopically by alteration in liver tissue architecture. The administration of liver toxicant causes, hemorrhage, congestion, necrosis, edema and remarkable blood vessel dilation. Moreover, honey exhibited protective action against this haloalkane in tissue architecture as the severity of liver tissue alteration was significantly reduced ($p<0.05$). The expressional pattern of P53 protein in groups treated with CCl_4 only as well as honey plus CCl_4 was statistically insignificant. In conclusion, this study reveals that natural honey has a remarkable protective effect against CCl_4-induced liver toxicity at antioxidant enzyme, histological and protein expression level.

Key words: Honey, Carbon tetrachloride, Liver toxicity, Antioxidant activity, Histopathological alteration.

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INTRODUCTION

Carbon tetrachloride (CCl_4) is a well-known liver toxin and its molecular mechanism behind in liver damage has been properly studied and proven satisfactorily[1]. The CCl_4-induced liver toxicity is the main reason of hepatic dysfunction as it alters the xenobiotic metabolizing system of hepatocytes, so the common use of this haloalkane has been restricted[2]. This haloalkane leads to the formation of highly toxic free radicals, accountable for attacks on unsaturated fatty acids of phospholipids present in cell membrane. This reaction sequence finally leads to lipid peroxidation in the hepatocytes[3]. The CCl_4-induced liver damage is also characterized by progressive tissue injury including inflammation followed by centrilobular hepatic necrosis, fibrosis as well as cirrhosis[3,4]. Furthermore, exposure of this liver toxicant causes elevated reactive oxygen species (ROS) production leading to pathogenesis including degeneration of the liver and kidneys.

The natural products have shown incredible sources of antioxidants, so being efficient therapeutic agents and some of these products prevent liver damage by scavenging free radicals and reactive oxygen species. In this regard, honey has been used since ancient times for the treatment and cure of different diseases. The natural honey is a dietary antioxidant as its constituents possess good redox potential[4,5]. It is a mixture of various compounds like flavonoids, vitamins, minerals, enzymes and proteins and such ingredients play a role in inhibition of pathogenesis through modulating cell signaling pathways.

Previous finding has reported the amelioration of oxidative stress noted after honey administration besides significant reduction in enlarged hepatocytes and edema. In addition to this, honey treatment leads to the restoration of bile canaliculi dilation and decreases the number of apoptotic cells[6]. In another study, the results have revealed that honey treatment reverse the changes in glutathione level, as well as the histopathological alterations induced by N-ethylmaleimide[7].

In the present study, hepatoprotective effects of natural honey against CCl_4-induced liver damage was evaluated through antioxidant status, histopathology and the expressional pattern of some cell-signaling proteins.

MATERIALS AND METHODS

Honey

The natural honey was purchased from Buraydah market, Qassim, Saudi Arabia and its purity was properly checked. It was diluted with water and applied through feeding bottles with concentration of 400 mg/kg/mouse during the time of treatment.

Animals

Male albino mice, 5-7 week old with a body of about 23-28 g each, were purchased from King Saud

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University, Saudi Arabia. The animals were properly checked to be free from any disease. The animals were acclimatized for one-week in animal house at an ambient temperature of 23±2 °C and a relative humidity of 45-55% with 12-h dark/light cycle. The animals were allowed to access rodent chow and tap water freely during acclimatization. The animals were closely monitored before the start of experiment.

Grouping of mice and experimental design

Thirty-two mice were selected and randomly assigned to four experimental groups with 8 mice in each group. The mice were handled properly as per the guidelines of WHO for animal handling. The experimental design was planned for twelve weeks. The name of the groups and the treatment method is as:

Group 1: (Normal control): The animals received water and normal mice chow throughout ten weeks.

Group 2: (Honey treated): The mice received only honey (400 mg/kg b.w, 4 times/week), water and normal mice chow.

Group 3: (Disease Control): The mice were treated with CCl_4 (0.04 ml of 40% solution of CCl_4 in olive oil) orally by gavage 4 times/week [8], water and normal mice chow.

Group 4: (CCl_4 plus honey treated): The mice were treated with CCl_4 (0.04 ml of 40% solution of CCl_4 in olive oil) and received honey (400 mg/kg b.w, 4 times/week), water and normal mice chow.

Measurement of serum biochemical markers

The blood samples from all the mice were collected at the time of sacrifice and allowed to clot at room temperature for 30 min and were centrifuged at 2000 *g* for 15 min at room temperature. The serum fraction was collected and refrigerated for further use. The level of aminotransferases: alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were measured.

Measurement of antioxidant enzymes/ total antioxidant capacity

The antioxidant enzymes including catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) were measured in each group of mice. The total antioxidant capacity was measured by using trolox kit (Abcam, UK).

Measurement of the serum IL-1β, TNF-α, and C-reactive protein (CRP) Levels

The blood samples were collected from each experimental group and the serum was separated. The concentrations of serum cytokine IL-1β, TNF-α, and C-reactive protein (CRP) levels were determined by using Abcam (Cambridge, UK) kits.

Histopathological analysis

Liver tissues from all the animals were excised at the time of sacrifice, for the analysis of Hematoxylin and Eosin staining. The liver from each animal were immediately fixed in 10% formalin, embedded in paraffin, cut into 5-6 µm sections. Hematoxylin-eosin (H&E) staining was performed to analyze the alterations in the liver tissue under a light microscope accordingly.

Immunohistochemistry

The expression of different types of proteins including HER-2 (human epidermal growth factor receptor 2), and p53 was evaluated through immunohistochemistry staining by earlier described method[9]. Deparaffinzation of the tissue sections were done by xylene and endogenous peroxidase used as blocking agent (Abcam, UK). Monoclonal antibodies of HER-2, and p53 (Abcam, UK) were used as primary antibodies. Secondary and tertiary antibodies were used for overnight at 4°C. Finally, diaminobenzidine (DAB) processing step was performed on the sections and counterstained with hematoxylin was made. The tissue was considered as positive staining for each marker when more than 5% of the stained cells showed positive expression for marker or less than 5% expression was considered as negative control. All the slides were observed under light microscope and results was interpreted accordingly.

TUNEL assay

Terminal deoxynucleotidyl transferase mediated dUTP nick end-labelling assay was performed to evaluate the apoptotic cells by apoptosis detection kit, Abcam, UK. All the steps were followed as per the guidelines provided with the kit. All the slides were observed, results were interpreted and the photographs were taken under light microscope.

Statistical analysis

All data are expressed as the mean ± SEM. The statistical analysis was performed by SPSS software by utilizing analysis of variance. The criteria for statistical significance was $p<0.05$.

RESULTS

Effect of honey on serum biochemical parameters

Serum ALT, AST and ALP activities were significantly increased in CCl_4 treated group (disease control, group 3) as compared with normal control groups (group 1) ($p<0.05$) (Figure 1). Treatment of animals with honey only (group 2) did not alter these enzyme activities. The increase in the enzyme activities were also noticed in group 4 animals (CCl_4 plus honey treated group), but the level of these enzymes was markedly lesser as compared to disease control group (Figure 1).

Effect of honey on antioxidant enzymes/total antioxidant capacity

As shown in Figure 2, the amount of GPx, SOD and CAT were significantly reduced in disease control group (group 3), i.e., the animals treated with CCl_4 only, as compared to normal control mice (group 1) and honey only treatment group (group 2) ($p<0.05$). Honey treatment significantly restored the level of these antioxidant enzymes in group 4 animals i.e. the mice intoxicated with CCl_4 besides treated with honey.

The total antioxidant status, examined by trolox equivalent capacity method, also indicated that treatment with CCl_4 only reduced the total antioxidants capacity significantly as compared to normal control, but treatment with honey in addition to CCl_4 significantly restores the antioxidant status (Figure 2).

Measurement of the inflammatory marker

The level of inflammatory markers including IL-Iβ, TNFα and C-reactive protein (CRP) was measured in all groups. It was noted that level of these markers were high in the CCl_4 treated group. However, honey treatment reduced the levels of these markers and the difference in the level of inflammatory markers in the honey plus CCl_4 treated group and the CCl_4 treated group only was statically significant ($p<0.05$) (Figure 3).

Evaluation of the liver tissue alterations through Hematoxylin and Eosin staining

The liver tissues from all the experimental groups were analyzed through H&E staining and the histological findings were compared

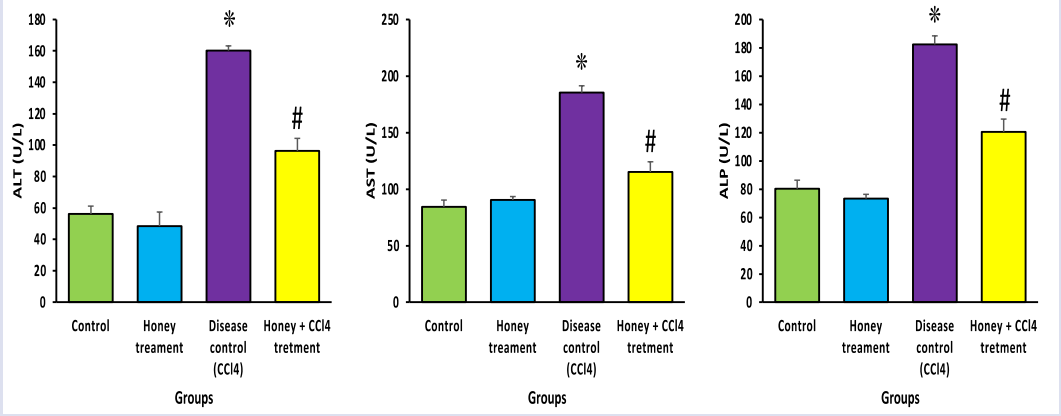

Figure 1: Effect of natural honey on serum liver function enzymes. Hepatic marker enzymes significantly raised in group 3 animals induced with CCl_4 and these enzymes decreased in group 4 (Honey + CCl_4-treated) animals significantly ($p<0.05$).

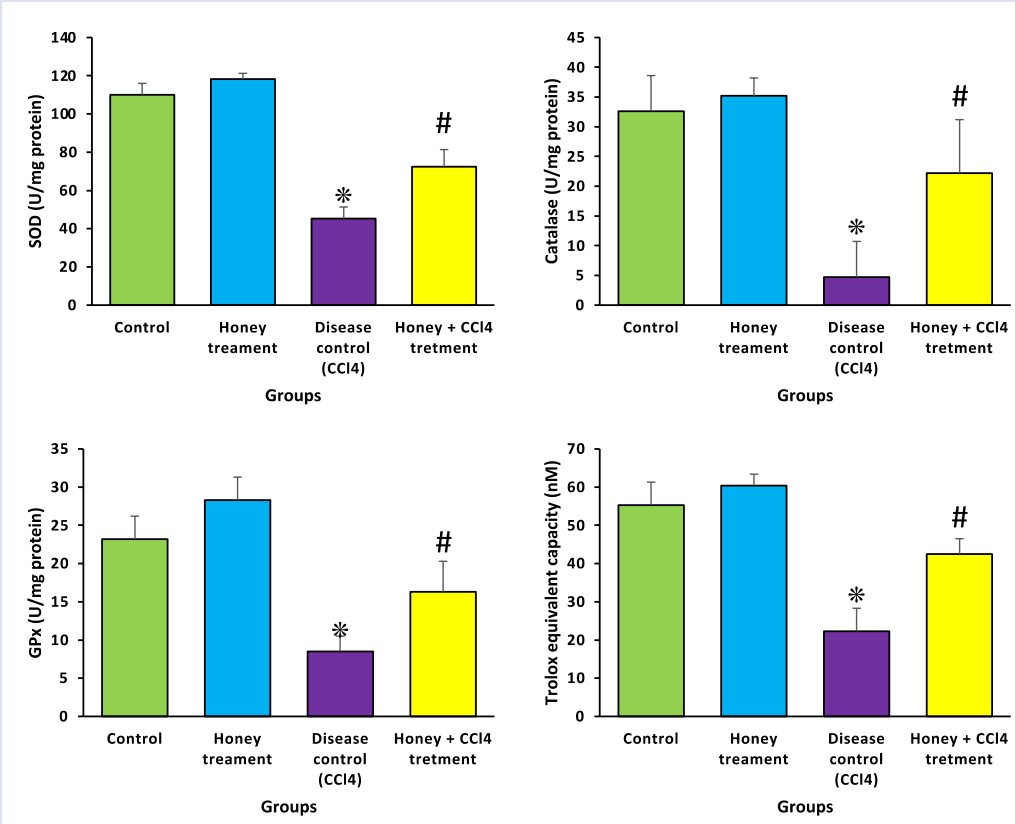

Figure 2: Effect of honey on antioxidant enzymes and total antioxidant capacity. The antioxidant enzymes (SOD, CAT and GPx) and the total antioxidant capacity significantly decreased by CCl_4 induction (group 3). Treatment with honey restored these enzymes significantly ($p<0.05$) in group 4 animals, which were treated with CCl_4 but in parallel treated with honey.

accordingly (Figures 4 a-d). The disease control mice (group 3) showed severe alteration in liver tissue architecture like hemorrhage, congestion and loss of hepatocytes, necrosis, edema and remarkable blood vessel dilations. While the treatment with honey in presence of CCl_4 toxication (group 4), the liver tissue alteration was significantly less as compared to disease control group.

Effect of honey treatment on cell signaling proteins expression

Expression of HER-2 protein

The expression of cell signaling proteins HER-2, was evaluated to get a clear picture about the protective role of honey against CCl_4-induced

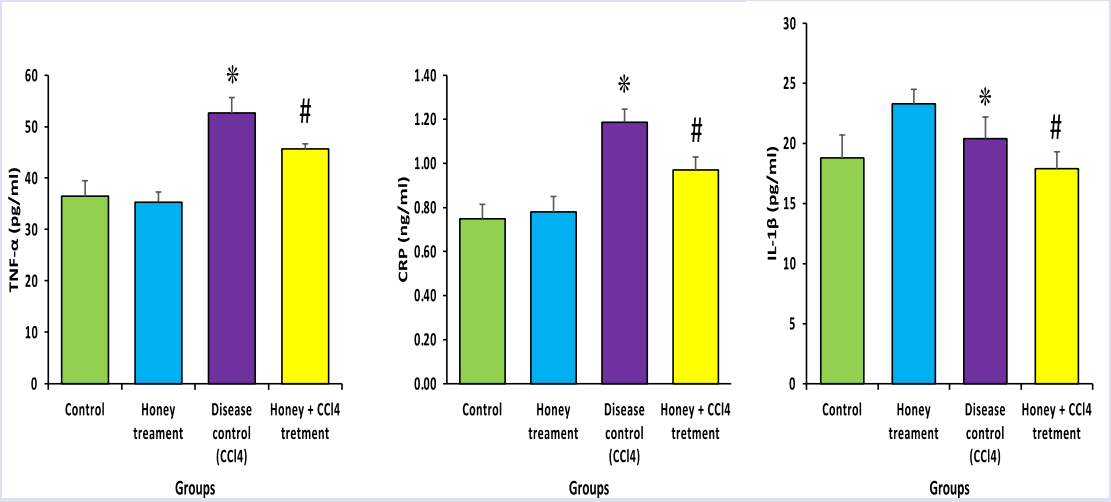

Figure 3: The levels of different inflammatory markers were found to be increased in group treated with CCl_4. However, OFPE reduced the levels of these markers. The values represent the mean ± SEM, with n=8 animals in each group. The statistically significant differences are indicated as hashtag (#) indicates significance at $p<0.05$ compared to control group and asterisk (*) indicates significance $p<0.05$ compared to the disease control.

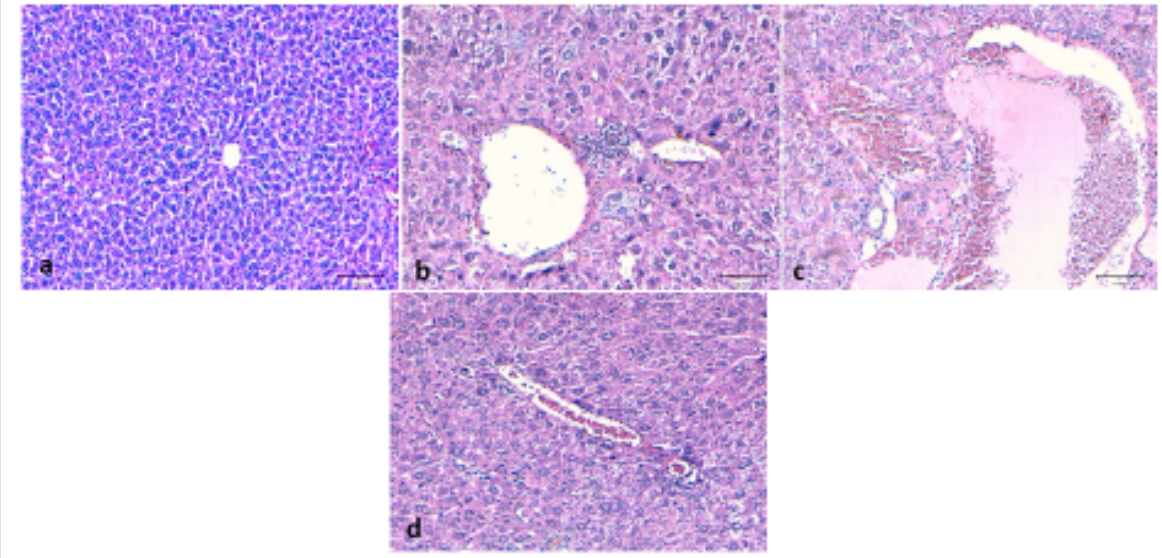

Figure 4: Photomicrographs of sections in liver of mice (H&E X40) showing the normal architecture of hepatocytes of control group (a). CCl4- treated mice showed loss of architecture, hemorrhage, congestion, necrosis, edema and remarkable blood vessel dilations (b-c). While the treatment with honey in presence of CCl_4 showing the liver tissue alteration was significantly less as compared to disease control group (d).

liver toxicity. HER-2 protein expression was high in all the experimental groups except normal control group and only honey treated group (Figures 5a-c). The high expression of HER-2 was noticed in CCl_4-treated group and Her-2 protein expression was also noticed in group 4 (animals treated with honey in presence of CCl_4-induction), but the intensity of expression was low as compared to disease control group. The difference in expressional pattern of HER-2 in control group and CCl_4-treated group was statistically significant ($p<0.05$).

Expression of p53

The p53 protein expression was not observed in normal control group, whereas its expression was high in group 3 animals as well as group 2 animals (Figures 6 a-c). The expressional pattern of P53 protein in groups treated with CCl_4 only as well as honey plus CCl_4 was statistically insignificant ($p>0.05$).

Apoptotic index

Apoptosis was evaluated in any experimental group including control and disease control group (group 3) and honey only treatment group (group 2) (Figures 7a-c). Apoptosis was seen in diseases control group whereas other did not show apoptosis.

DISCUSSION

Carbon tetrachloride is a well-known hepatotoxin and its metabolites alter the xenobiotic metabolizing system of liver. Different natural products as a whole or their individual constituents play an important role to withhold the destructive effect of CCl_4. Natural honey is a mixture of various compounds like flavonoids, vitamins, minerals, enzymes and proteins and such ingredients play a vital role in disease management through modulating biological activities. So, honey acts

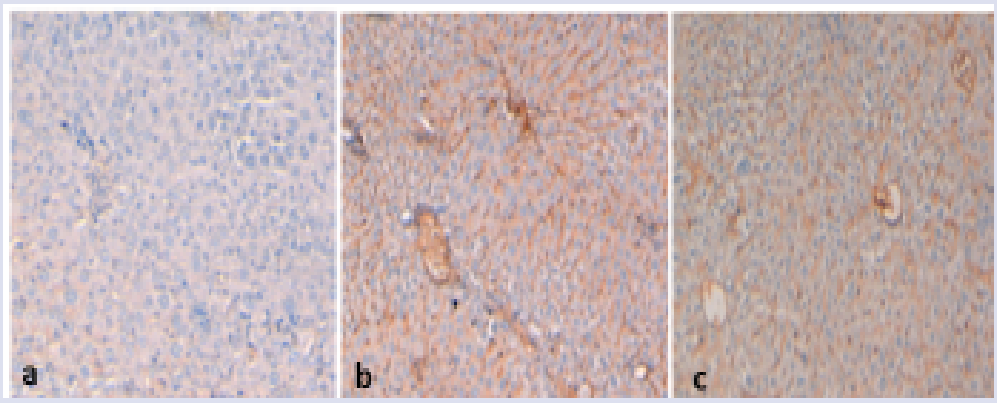

Figure 5: Her-2 protein expression in the liver was evaluated by immunohistochemistry staining (a-c). Her-2 staining was not detected or very low expression was observed in the control group: (a). CCl_4-treated group showed intense staining (b), whereas CCl_4 plus honey treated group also showed expression (c) but intensity was less as compared to CCl_4-treated group only. Moreover, Her-2 expression was not detected in honey only treated group.

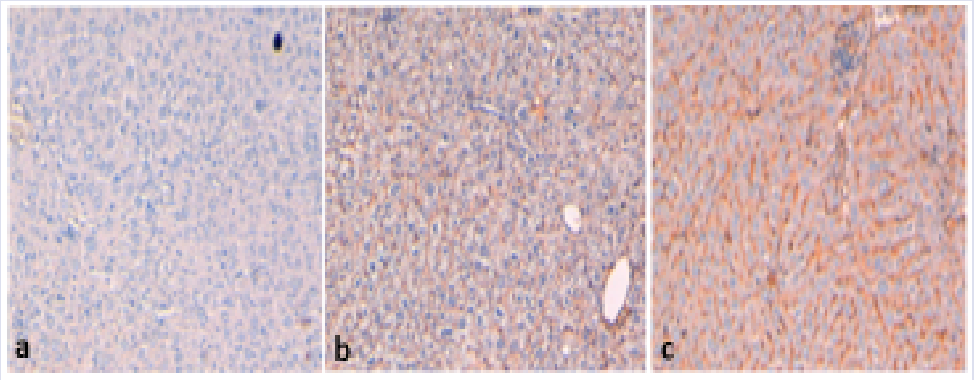

Figure 6: Undetectable level of p53 protein was noted in control group (a). High expression was detected in CCl_4-treated group (c). Moreover, PTEN expression was also detected in CCL_4 and honey treated group (b).

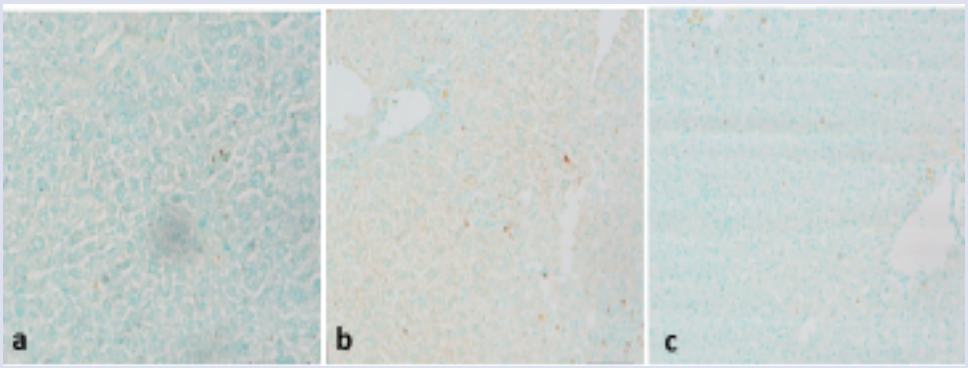

Figure 7: No apoptosis was seen in control group (a), CCl_4-treated group (b) and CCL_4 plus honey treated group (c).

as a free radical scavenger and protects the liver from oxidative damage induced by toxic agents.

In the current study, it was observed that the activities of liver function enzyme (ALT, AST and ALP) significantly increase in CCl_4 treated group as compared to the normal control group. Moreover, the mice treated with honey in addition to CCl_4, had a significantly reduced the level of these enzymes toward the reference range (Figure 1). These results agree with the earlier study as it was reported that serum ALT and AST activity was significantly increased in CCl_4 treated groups as compared to the normal control[10].

In this regard, previous findings reported that *apes cerana* honey significantly improves the liver injury, as described by the decreased level of serum ALT, AST and inhibited malondialdehyde (MDA) content[11].

In addition to this, another study reported that honey and silymarin treatment prior to the administration of paracetamol significantly prevented the increase in serum level of hepatic function enzyme markers[12] and pre-treatment with sundarban honey showed significantly reduced levels of hepatic marker enzymes[13].

Due to the presence of phenolics, ascorbic acid and other antioxidants in honey[14], these molecules play a great role in the prevention of liver damage. The current study revealed that the amount of antioxidant enzymes like SOD, CAT and GPx were significantly reduced in the CCl_4 treated group as compared to the normal control group. Animals which were treated with honey in addition to CCl_4 toxication (group 3) significant restoration of these antioxidant enzymes as observed as compared to animals treated with CCl_4 only (Figure 2).

The previous findings were in accordance with the current findings and it was reported that the antioxidant status in liver such as the activities of SOD, CAT, GPx and the level of glutathione (GSH) were significantly decreased in (Acetaminophen) APAP treated animals. Pretreatment with honey and silymarin before the administration of APAP significantly reduced the oxidative stress[15]. Another study demonstrated that *A. cerana* honey promoted SOD and glutathione peroxidase (GSH-Px) activities significantly[11].

The changes in liver function enzymes and the antioxidant potential by the CCl_4 induction are in parallel to the tissue injury including inflammation followed by necrosis, fibrosis as well as cirrhosis[3,4]. In this study, it was noticed that CCl_4-treated mice showed tissue alterations including hemorrhage, congestion, and the loss of hepatocyte architecture, edema and blood vessel dilation. Whereas, the severity of liver tissue alteration in animals treated with honey in addition to CCl_4-intoxication, was significantly lesser than animals treated with CCl_4 only.

The hepatotoxic action of CCl_4 is closely associated with its short lived reactive intermediates that also cause lipid peroxidation[16]. An interesting finding has reported that hepatic tissue treated with honey showed normal architecture while the liver supplemented with honey in addition to melamine showed slight degree of necrosis and clear accumulation of hepatic strands[17]. In parallel, another study has confirmed that the gross lesions were not seen in hepatic tissue of rats in control and aflatoxin plus honey treated groups[18]. Several other findings have proven that the medicinal plants and their specific constituents have different therapeutic roles through the activation and inactivation of various cell signaling pathways[19-21].

The human epidermal growth factor (HER-2/neu) is a proto-oncogene and it is located on chromosome 17q21 that encodes ErbB-2[22]. The activation of HER-2 plays a vital role in cell proliferation, cell differentiation, inhibition of apoptosis, and tumor progression[23-25]. In this study, CCl_4 group showed increase HER-2 expression whereas, the honey treated group and normal control group did not show any expression. The highest expression of HER-2 was noted in CCl_4 treated group and HER-2 expression was also noted in CCl_4 plus honey treated group but the intensity of the expression was less as compared to disease control group (group 3) (Figure 4). The previous findings have also reported that the frequency of positive samples and the intensity of ErbB-2 staining was low in the normal liver and was progressively higher in samples from patients with chronic hepatitis, cirrhosis, and highest in peritumor liver[26].

The PTEN tumor suppressor has been identified through homozygous deletion mapping of the human chromosome 10q23 in cancer[27,28]. The loss of PTEN protein has been noticed in several types of tumor. The present study reported that the loss of PTEN expression was seen in CCl_4 treated group whereas PTEN protein showed high expression in CCl_4 plus honey treated group and only honey treated group (Figure 5).

In this vista, the natural products or medicinal plants show pivotal role in the upregulation of PTEN gene and finally inhibit the pathogenesis of diseases. In this regard, the previous finding reported that Curcumin acted on HSCs and revealed it regulated miRNA-mediated control of DNA methylation and controlled fibrogenesis at an epigenetic level through upregulation of PTEN[29]. In another study, it is revealed that withaferin A, one of the withanolides isolated from the *Withania somnifera* plant showed role in the protection against liver injury in mice treated with APAP by inducing Nrf2 signaling, particularly depending on PTEN/P13K/Akt cascade[30].

p53 is a nuclear transcription factor and it transactivates numerous target genes involved in the induction of cell cycle arrest and/or apoptosis[27-30]. This study reports that p53 protein expression was not observed in the normal control group, whereas the expression was high in CCl_4 treated group as well as in honey plus CCl_4 (group 4). The expression pattern of p53 protein in CCl_4 only treated group as well as honey plus CCl_4 treated group was statistically insignificant (Figure 6). The previous findings have reported that streptozotocin (STZ) exposure significantly increases the p53 protein level and Curcumin treatment attenuate such activation. Therefore, it can be concluded that STZ exposure could effectively induce p53 activation[31]. Another finding, based on honey reported that hepatocytes of control group showed low expression of p53, whereas a high expression was noticed in liver sections of rats treated with DEN as the liver carcinogen. Moreover, the liver sections of the rats injected with DEN and treated with honey showed the positive stain in some hepatocyte nuclei but less than that of the DEN carcinogen treated animals[32]. In the current study, no apoptotic body was observed in any experimental group. In this regards, previous finding reported that apoptosis index was noted in cancerous cases and it was 28% patients showed high apoptotic while 72% showed low index[33].

CONCLUSION

This study clearly reveals that CCl_4-induction leads to liver toxicity that is characterized by a notable increase in hepatic function enzyme level. In addition to this, CCl_4-induction causes a decrease in antioxidant enzyme/status and causes significant histopathological alterations of liver tissue. The findings of this study clearly demonstrate that natural honey has a good therapeutic effect in terms of improving the antioxidant enzyme level and decreases the hepatic functions enzymes towards reference range in CCl_4-induced liver toxicity.

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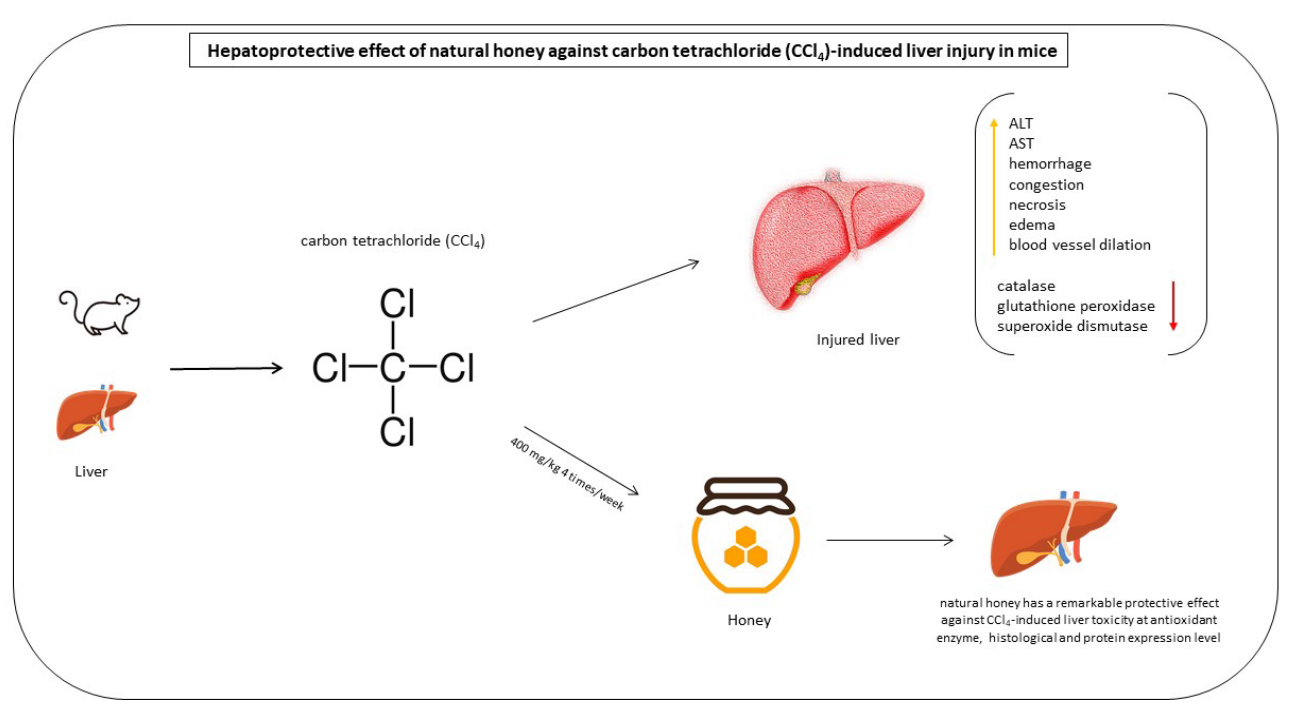
GRAPHICAL ABSTRACT



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