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THERAPEUTIC EFFECT OF GINGER, ALOE, BEE HONEY AND THEIR MIXTURE ON CHRONIC LIVER DAMAGE AND FIBROSIS INDUCED BY CCl_4 IN RATS

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ABSTRACT

The purpose of this study was to evaluate the hepatoprotective and antifibrotic potential of ginger, aloe, bee honey and their mixture on chronic liver injury induced by CCl_4 for 8 weeks. The results exhibited that the increase of serum alanine aminofransferase (sALT), serum aspartate aminotransferase (sAST), alkaline phosphatase (sALP) activities, total and direct bilirubin as well as liver homogenate thiobarbituric acid reactive substances (TBARS) in CCl_4 liver injury were significantly reduced by treatment with ginger (0.1g/kg b.w.), aloe (0.5g/kg b. w.), bee honey (34 g/kg b. w.) and their mixture, five times in a week. The aforementioned materials reduced the collagen content by 60%, 66.7%, 62.85% and 68.65%, respectively. The results were comparable to silymarin (25mg/ kg b.w.).

Keywords: Thyme plant, Ginger rhizomes, Bee honey, liver collagen, TBARS, ALT, AST, ALP activities, Rats.

INTRODUCTION

Clinical research confirmed the efficacy of several plants in the treatment of liver disease such as cirrhosis, fatty liver and chronic hepatitis (Scott - Luper, 1998). The liver of tumor - bearing animals has involved as a reliable model in the study of malignant transformation and intervention by chemopreventive agents which intercept quantitative changes in hepatic enzymes and metabolites induced by the presence of an extrahepatic tumor (Johnson, 1997). Medicinal plants have received growing attention in recent years as potential chemopreventive agents.

Hepatic stellate cells play a central pathogenic role in liver fibrogensis. They response to some fibrotic influences such as carbon tetrachloride, chronic ethanol exposure, they proliferate and transform into myofibroblasts which are responsible for the deposition of collagen fiber in liver (Fuchs *et al.*, 1997).

In the present study, we investigated the effects of *Aloe vera* gel, ginger rhizomes, bee honey and their mixture on hepatotoxic damage, their antifibrotic effect in rats model of chronic liver damage induced by multiple injection with carbon tetrachloride (CCl_4) for 8 weeks. The liver damage was assessed by measuring the serum total and direct bilirubin contents, alanine - and aspartate aminotransferase (ALT and AST) and alkaline phosphatase (ALP) activities. Also, hepatic collagen and thiobarbituric acid reactive substances (TBARS) were determined in liver homogenate as well as histopathological examination. We used the hepatoprotective effect of silymarin for comparison.

MATERIALS AND METHODS

Source of materials

Ginger (*Zingiber officinale* Roscoe) was purchased from local market, dried thoroughly and finally powdered. Nopal (*Aloe vera*) and bee honey (bees fed on citrus flowers) were obtained from Ormane garden, Cairo University Street and Faculty of Agriculture, Cairo University, respectively. *Aloe vera* gel is the colorless mucilaginous gel obtained by stripping the parenchymatous cells in the fresh leaves (Tyler, 1993).

Chemicals and Reagents

Carbon tetrachloride (CCl_4, Fine Chemie KG., Sebnitz, Germany); silymarin (local pharmacy); Kits of total and direct bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), collagen and TBARS (Biodiagonstic Co. 29 EL-Tahreer Street, Dokki, Giza, Egypt). All other reagents of analytical grade.

Animals

A number of 56 male albino rats weights ranged between 200-250 g were obtained from the Research Institute of Ophthalmology, Giza, Egypt.

Nutritional experiments

The basal diet consisted of corn starch (65%), casein (15%), corn seed oil 10%, salt mixture (40%), vitamin mixture (1%) and cellulose (5%) was prepared according to A. O .A. C (1975). Experimental rats were fed on basal diet for 7 days and randomly divided into 7 groups .The 1st. group (8 rats) was fed on a basal diet for another 56 days and considered as normal control rats. The rats of 2nd, 3 rd, 4 th, 5 th, 6 th, and 7 th groups (8 rats) were received CCl_4 (40%) in paraffin oil (3ml /kg b. w.) twice at week for 8 weeks to induce chronic liver damage in these rats. The 2nd group was pretreated until the end of the experiment treated with CCl_4 (40%) and considered as positive control rats. The 3rd, 4 th, 5 th and 6 th groups were orally treated with silymarin as a drug (25 mg /kg b. w.), ginger roots (0.1 g /kg b.w.), bee honey (34g /kg b w.), aloe gel (0.5g /kg b.w.) 5 times at weak for 8 weeks, respectively. The same design was adopted for 7th rat group using a mixture from aloe gel, ginger roots and bee honey at the same doses mentioned before.

Blood samples were withdrawn from the orbital plexus under ether anesthesia after 24 h, 3, 6 and 8 weeks and centrifuged at 3000 rpm for 10 min., and then the sera were kept in a deep freeze at - 20°C until analysis.

At the end of the experiment (8 weeks) the rats were Killed by decapitation and the liver organ was excised and washed with ice-cold isotonic saline solution (0.15 M KCl) and stored at -20°C until analysis.

Assessment of some blood constituents

The activities of serum alanine aminotransferase (ALT, EC 2.6.1.2), serum aspartate aminotransferase (AST, EC 2.6.1.1) and serum alkaline phosphatase (ALP, EC 3.1.3.1) were determined according to Bergmeyer and Harder (1986), Nilkinson (1976) and Belfield and Goldberg (1971),

respectively. The total and the direct bilirubin were estimated by the method of Doumas *et al.* (1987).

Preparation of liver samples for measurement of TBA values

The rat liver organ was homogenized according to the method of Bwcher and Grrahan (1956). The homogenate was filtered through 5 layers of muslin at 4°C and centrifuged at 5000 rpm for 15 min. to isolate the nuclei. The suppernatant was stored in deep freezer at – 20°C until analysis.

Hepatic thiobarbituric acid reactive substances (TBARS) were determined in liver homogenate according to Sidwell *et al.* (1954) as an evidence of lipid peroxidation occurrence.

Measurement of antifibrotic property

Hydroxyproline content was measured in the liver to estimate the hepatic collagen content according to laitinen *et al.* (1974) as follows:

At first, liver tissues were dehydrated by 95% alcohol for 5-6 h, and defatted by acetone for two days, then dried in the oven at 110°C and ground into powder. Forty mg of liver powder were placed in a test tube, then 3 ml of HCl (6M) were added and hydrolyzed at 110°C for 12 h. Hydrolysates were filtered and diluted to 50 ml and the solution was adjusted to pH 6. Two ml of the dilution and 1 ml of 0.05 M chloramines- T were placed in a new tube, shaken vigorously and left at room temperature for 20 min; followed by adding 1 ml of 10% p- dimethylaminobenzaldehyde, incubated at 60°C for 20 min. Finally, the tube was cooled in an ice bath for 5 min. to stop the reaction, and then recorded at 550 nm against a reagent blank by means of a spectrophotometer.

Histopathological study

At the end of the experiment period, the rats were killed by decapitation and the liver organ was removed, stored in 10% neutral formalin and embedded in paraffin wax. The organ was sectional at the thickness of 5.6 microns and stained with haematoxylin and eoxin according to Culling (1965). Tissue sections were then examined using ordinary microscope for histological evaluation.

Statistical analysis

The present data were subjected to analysis of variance and the least significant difference (L. S. D.) test was calculated to allow comparison between the average values of the studied factors (Snedecor and Corchran, 1972).

RESULTS AND DISCUSSION

Serum bilirubins types

Data in Tables 1 and 2 show the effect of ginger (*Zingiber officinale*), nopal (*Aloe vera*), bee honey and their mixture on total and direct bilirubins of rats with injury liver. In case of carbon tetrachloride control rat group at all the times of the experiment, produced a significant elevating of serum total and direct bilirubins as compared with the normal control. Upon the administration by ginger, aloe, bee honey and their mixture led to lowering the total and direct bilirubin concentrations, as well as silymarin at all the periods of the experiment as compared with carbon tetrachloride control rats.

Table (1): Effect of *Zingiber officinale*, *Aloe vera*, bee honey, their mixture and silymarin on the level of serum total bilirubin (mg/dL) of rats with liver damage.

Treatment	Blood withdrawal period (week)			
	24 h	3 week	6 week	8 week
Normal control	$0.70^{d} \pm 0.02$	$0.48^{d} \pm 0.04$	$0.85^{b} \pm 0.08$	$0.92^{c} \pm 0.08$
Carbon tetrachloride control (3 ml/kg b.w.)	$1.29^{a} \pm 0.13$	$5.55^{a} \pm 0.09$	$1.85^{a} \pm 0.03$	$2.86^{a} \pm 0.09$
Silymarin (25 mg/kg b.w.)	$0.42^{e} \pm 0.01$	$0.88^{c} \pm 0.05$	$0.77^{b} \pm 0.01$	$1.13^{b} \pm 0.18$
Zingiber officinale (0.1 g/kg b.w.)	0.85d ± 0.02	$1.00^{b} \pm 0.10$	$0.84^{b} \pm 0.09$	$0.94^{c} \pm 0.08$
Aloe vera (0.5 g/kg b.w.)	$2.65^{c} \pm 0.21$	$1.17^{b} \pm 0.01$	$0.79^{b} \pm 0.02$	$1.31^{b} \pm 0.03$
Bee honey (34g/kg b.w.)	$0.76^{d} \pm 0.03$	$0.81^{c} \pm 0.10$	$0.67^{b} \pm 0.03$	$1.53^{b} \pm 0.02$
Mixture (*Zingiber officinale* + *Aloe vera* + bee honey)	$1.62^{b} \pm 0.10$	$1.01^{b} \pm 0.04$	$0.78^{b} \pm 0.04$	$1.25^{b} \pm 0.04$
The value of L. S. D. at 5%	0.71	0.21	0.22	0.46

The data are expressed as mean values ± standard error.

Table (2): Effect of *Zingiber officinale*, *Aloe vera*, bee honey, their mixture and silymarin on the level of serum direct bilirubin (mg/dL) of rats with liver damage.

Treatment	Blood withdrawal period (week)			
	24 h	3 week	6 week	8 week
Normal control	$0.51^{d} \pm 0.06$	$0.31^{d} \pm 0.01$	$0.21^{c} \pm 0.01$	$0.39^{d} \pm 0.01$
Carbon tetrachloride control (3 ml/kg b.w.)	$1.24^{a} \pm 0.10$	$5.24^{a} \pm 0.10$	$1.01^{a} \pm 0.12$	$1.34^{a} \pm 0.10$
Silymarin (25 mg/kg b.w.)	$0.31^{d} \pm 0.02$	$0.53^{c} \pm 0.04$	$0.53^{bc} \pm 0.01$	$0.62^{c} \pm 0.01$
Zingiber officinale (0.1 g/kg b.w.)	$0.91^{b} \pm 0.01$	$0.82^{b} \pm 0.02$	$0.75^{b} \pm 0.00$	$0.71^{c} \pm 0.01$
Aloe ver7a (0.5 g/kg b.w.)	$0.63^{c} \pm 0.09$	$0.70^{b} \pm 0.02$	$0.68^{ab} \pm 0.04$	$1.13^{a} \pm 0.12$
Bee honey (34g/kg b.w.)	$0.35^{d} \pm 0.14$	$0.50^{c} \pm 0.02$	$0.55^{bc} \pm 0.09$	$0.93^{b} \pm 0.02$
Mixture (*Zingiber officinale* + *Aloe vera* + bee honey)	$1.31^{a} \pm 0.12$	$0.94^{b} \pm 0.00$	$0.65^{ab} \pm 0.09$	$0.97^{b} \pm 0.04$
The value of L. S. D. at 5%	0.34	0.33	0.33	0.35

The data are expressed as mean values ± standard error.

The data after 6 and 8 weeks of the experiment indicate that the efficacy of all treatments was equilibrity efficiency the silymarin in the decrease the levels of the bilirubin types and as approximate normal control. These data are on line with those of Krisztina *et al.* (2002).

These findings beside the results of the present study suggest adding these materials or their mixture to foods to maintenance the human health.

Alanine-, aspartate aminotransferases (ALT and AST) and alkaline phosphatase (ALP) activities

In order to evaluate the natural sources (ginger, aloe, bee honey and their mixture) as hepatoprotective potential as well as silymarin as drug in chronic liver damage during 8 weeks, we assessed the differences among groups at 24 h, 3, 6 and 8 weeks. Table 3, 4 and 5 show the changes of serum enzymes (ALT, AST and ALP) activity at all the times.

Table (3): Effect of *Zingiber officinale*, *Aloe vera*, bee honey, their mixture and silymarin on alanine aminotransferase activity (IU/L) of rats with liver damage.

Treatment	Blood withdrawal period (week)			
	24 h	3 week	6 week	8 week
Normal control	$23.67^{d} \pm 0.44$	$26.00^{d} \pm 0.00$	$23.25^{e} \pm 0.20$	$21.00^{e} \pm 0.21$
Carbon tetrachloride control (3 ml/kg b.w.)	$56.50^{a} \pm 0.00$	$360.30^{a} \pm 7.68$	$390.00^{a} \pm 1.45$	$540.30^{a} \pm 3.52$
Silymarin (25 mg/kg b.w.)	$60.40^{ab} \pm 0.00$	$210.00^{b} \pm 3.46$	$265.70^{cb} \pm 1.20$	$433.30^{b} \pm 0.88$
Zingiber officinale (0.1 g/kg b.w.)	$36.50^{cd} \pm 0.66$	$200.00^{bc} \pm 1.15$	$156.30^{ad} \pm 1.85$	$116.70^{d} \pm 1.76$
Aloe vera (0.5 g/kg b.w.)	$50.50^{b} \pm 1.2$	$230.00^{b} \pm 3.21$	$224.6^{b} \pm 2.60$	$483.30^{b} \pm 0.88$
Bee honey (34g/kg b.w.)	$48.00^{c} \pm 0.00$	$143.30^{c} \pm 4.25$	$130.00^{d} \pm 1.45$	$483.30^{b} \pm 2.02$
Mixture (*Zingiber officinale* + *Aloe vera* + bee honey)	$48.0o^{c} \pm 0.00$	$143.30^{c} \pm 2.08$	$171.30^{c} \pm 2.40$	$350.00^{c} \pm 2.40$
The value of L. S. D. at 5%	2.28	11.75	5.51	7.19

The data are expressed as mean values ± standard error.

The results in Tables 3 and 4 indicate that the normal control serum values of ALT and AST in rats were found to be 23.67, 26.00, 23.25 and 21.00; 23.30, 25.30, 33.00 and 29.50 after 24 h, 3, 6 and 8 weeks, respectively. They raised significantly to respective values of 65.50, 360.30, 390.00 and 540.30; 142.30, 369.60, 598.60 and 932.30 after administration of a toxic dose of CCl_4 (3 ml/kg b. w.). Also, we observed that the ALT and AST activities were significantly higher in all of the CCl_4 - treated groups (control, silymarin, ginger, aloe, bee honey and their mixture) than the normal control group after 24h from first administration.

After 3, 6 and 8 weeks, all treatments including silymarin (25 mg/kg b.w.), ginger (0.1 g/kg b. w.), aloe (0.5 g/kg b. w.), bee honey (34 g/kg b. w.) and their mixture significantly reduced the increasing tendency of ALT and AST activities. We noted that ginger rihsomes demonstrated better hepatoprotective effect, followed by the mixture than other treatments as well as silymarin at the end of the experiments.

Table (4): Effect of *Zingiber officinale*, *Aloe vera*, bee honey, their mixture and silymarin on serum aspartate aminotransferase (AST) activity (IU/L) of rats with liver damage.

Treatment	Blood withdrawal period (week)			
	24 h	3 week	6 week	8 week
Normal control	$23.30^{d} \pm 0.66$	$25.30^{c} \pm 0.66$	$33.00^{e} \pm 0.57$	$29.50^{e} \pm 0.66$
Carbon tetrachloride control (3 ml/kg b.w.)	$142.30^{a} \pm 1.20$	$369.60^{a} \pm 0.78$	$598.60^{a} \pm 0.66$	$932.30^{a} \pm 1.01$
Silymarin (25 mg/kg b.w.)	$89.00^{c} \pm 0.00$	$227.00^{bc} \pm 0.57$	$349.00^{c} \pm 0.57$	$535.00^{c} \pm 0.57$
Zingiber officinale (0.1 g/kg b.w.)	55.30 ± 1.17	$230.30^{bc} \pm 0.00$	$201.30^{d} \pm 0.91$	442.00 ± 1.73
Aloe vera (0.5 g/kg b.w.)	$103.7^{b} \pm 1.00$	$261.50^{b} \pm 0.68$	$355.20^{c} \pm 0.61$	$655.30^{b} \pm 1.2$
Bee honey (34g/kg b.w.)	$113.53^{ab} \pm 0.74$	$220.60^{bc} \pm 1.20$	299.4 ± 0.42	$523.00^{c} \pm 1.52$
Mixture (*Zingiber officinale* + *Aloe vera* + bee honey)	$96.30^{c} \pm 0.88$	$237.20^{bc} \pm 1.27$	$441.30^{b} \pm 0.34$	$398.30^{d} \pm 0.88$
The value of L. S. D. at 5%	2.46	2.73	1.85	3.51

The data are expressed as mean values ± standard error.

Table (5): Effect of *Zingiber officinale*, *Aloe vera*, *bee* honey, their mixture and silymarin on serum alkaline phosphatase (ALP) activity (IU/L) of rats with liver damage.

Treatment	Blood withdrawal period (week)			
	24 h	3 week	6 week	8 week
Normal control	$78.20^{d} \pm 4.1$	$88.40^{c} \pm 1.02$	$60.50^{d} \pm 1.00$	$68.30^{c} \pm 1.05$
Carbon tetrachloride control (3 ml/kg b.w.)	$127.50^{a} \pm 1.00$	$306.20^{a} \pm 0.42$	$383.15^{a} \pm 1.00$	$435.50^{a} \pm 1.07$
Silymarin (25 mg/kg b.w.)	$120.00^{a} \pm 1.15$	$282.10^{c} \pm 0.44$	$353.00^{a} \pm 1.00$	$329.30^{a} \pm 0.85$
Zingiber officinale (0.1 g/kg b.w.)	$145.20^{c} \pm 1.07$	$184.54^{d} \pm 1.02$	$157.7^{c} \pm 1.02$	$330.60^{a} \pm 1.15$
Aloe vera (0.5 g/kg b.w.)	$135.00^{c} \pm 1.15$	$348.54^{b} \pm 1.02$	$284.54^{b} \pm 1.02$	$291.430^{b} \pm 1.07$
Bee honey (34g/kg b.w.)	$147.00^{b} \pm 0.58$	$117.10^{d} \pm 1.18$	$278.17^{b} \pm 1.02$	$254.61^{bc} \pm 1.12$
Mixture (*Zingiber officinale* + *Aloe vera* + bee honey)	$180.00^{b} \pm 0.58$	$392.01^{b} \pm 1.12$	$302.30^{ab} \pm 1.15$	$280.31^{b} \pm 1.12$
The value of L. S. D. at 5%	2.73	1.38	1.78	1.45

The data are expressed as mean values ± standard error.

Data in Table (5) show the increasing tendency of serum ALP at different times for each group. For the normal control group, there was no significant difference of ALP activity between different time points. For the other CCl_4 – induced groups including CCl_4 – treated control, ginger, aloe, bee honey and their mixture as well as silymarin for comparison, by using the same doses, sALP activity was significantly elevated compared with normal control. We found that the administration of mentioned materials and silymarin using the aforementioned doses resulted in improving serum ALP values which were significantly lower ($P < 0.05$) than those of toxic control at all the experiment. At the end of 8 weeks, aloe, bee honey and the mixture was more effective than silymarin for reducing the sALP activity when compared to the toxic control, this is due to the fact of being silymarin used for treatment of cirrhosis and not carcinoma. These results are in agreement with those of Uma *et al.* (2003) who found that oral administration of ginger ethanolic extract (200 mg / kg) significantly lowered sAST, ALT and ALP activities. Also, Fan *et al.* (1989) and Corsi et al. (1998) observed that the injection of 600 mg/kg/day, 3 times of *Aloe vera* resulted in lowering the elevated sALT induced by CCl_4 in mice or rats. It was also observed that the agent could protect hepatic cells from the CCl_4 – induced injury.

Thiobarbituric acid reactive substances (TBARS) and collagen

Data in Table (6) show the concentrations of liver TBARS and collagen contents in control and experimental rats at the end of the experiments (after 8 weeks).

Table (6): Effect of *Zingiber officinale*, *Aloe vera*, bee honey, their mixture and silymarin on hepatic thiobarbituric acid reactive substances (TBARS,n mol MDA/mg) and collagen content (mg/g) of rats with liver damage.

Treatment	Collagen	TBARS
Normal control	$6.20^{d} \pm 0.06$	$1.18^{c} \pm 0.11$
Carbon tetrachloride control (3 ml/kg b.w.)	$20.00^{a} \pm 0.58$	$2.1^{a} \pm 0.06$
Silymarin (25 mg/kg b.w.)	$10.33^{d} \pm 0.88$	$1.83^{b} \pm 0.08$
Zingiber officinale (0.1 g/kg b.w.)	$8.00^{c} \pm 0.58$	$1.80^{b} \pm 0.06$
Aloe vera (0.5 g/kg b.w.)	$6.66^{cd} \pm 0.33$	$1.86^{b} \pm 0.06$
Bee honey (34g/kg b.w.)	$7.43^{cd} \pm 0.06$	$1.60^{b} \pm 0.06$
Mixture (*Zingiber officinale* + *Aloe vera* + bee honey)	$6.27^{d} \pm 0.09$	$1.17^{c} \pm 0.09$
The value of L. S. D. at 5%	1.43	0.23

The data are expressed as mean values ± standard error.

Liver concentration of TBARS was significantly higher in CCl_4 – treated rats as compared with control ones. The supplementation by silymarin (25 mg/kg b. w.), ginger (0.1 g/kg b. w.), aloe (0.5 mg/kg b. w.), bee honey (34 g/kg b. w.) and their mixture significantly decreased the concentration of TBARS by about 12.86 %, 14.29 %, 11.43 5, 23.81 % and 44.29 %, respectively. From these results, it was observed that the mixture was more effective than silymarin and other treatments as curative and chemopreventive agents

against liver damage. These results are in line with those of Vaiyapuri and Namasivayam (2005) who found that ginger supplementation at the initiation stage and also at the post – initiation stages of carcinogenesis significantly reduced circulating lipid peroxidation and significantly enhanced the enzymic and non-enzymic antioxidant as compared to unsupplemented 1,2-dimethylhydrazine-treated rats.

The zerumbone (ZER), a topical ginger sesquiterpene has a significant ability to suppress oxidative stress possibly through induction of the endogenous antioxidants. Considering the importance of oxidative damage in carcinogenesis, the antioxidant effect of ZER can be explored as a cancer chemopreventive agent targeted towards inflammation related carcinogensis such as skin cancer and colon cancer (Yoshimasa *et al.*, 2004).

Table (6) elucidates the collagen content of the CCl_4 – damage, untreated group has extremely higher value than that of normal control group. On the other hand, silymarin (for comparison) ginger, aloe, bee honey and their mixture groups significantly reduced the content of collagen by 48.35%, 60%, 66.7%, 62.85% and 68.67%, respectively, when compared with the untreated CCl_4 liver - damage group. Finally, the mixture was more efficiency than silymarin and other treatments against liver damage. These results are in agreement with those of Jung-Chou (2000).

Histopatholgical examination

Microscopically, liver section of control, untreated rat revealed the normal histological structure of hepatic lobule which consists of central vein and concentrically arranged hepatocytes (Figure 1). Conversely, severe histopathological changes were observed in liver of rat treated with CCl_4, the liver showed hepatocellular carcinoma with pleomorphic hepatocytes, large foamy cells, typical and a typical mitotic figure of hepatocytes, intercellular connective tissue proliferation as well as marked inflammatory cells infiltration (Figure 2). Liver of rat treated with CCl_4 plus silymarin revealed hepatocllular carcinoma, fibrous connective tissue proliferation, proliferation of bile duct lining cells with formation of new bile ductoles. Moreover, liver of rat treated with CCl_4 plus ginger showed slight improvement in the histopathological picture, the liver showed proliferation of bile duct lining cells, vacuolar degeneration of some hepatocytes and necrosis of other hepatocytes (Figure 3). However, hepatocellular carcinoma with pleomorphic hepatocytes, foamy cells appearance, mitotic figures, congested blood capillaries as well as fibrous connective tissue stroma were noticed in examined liver of rat treated with CCl_4 bee honey. Moreover, marked histological alterations were noticed in liver of rat treated with CCl_4 plus *Aloe vera* as the liver showed hepatocellular carcinoma, vacuolations of some hepatocytes, congested blood vessels, hemorrhage and fibrous connective tissue stroma. On the other hand, marked improvement in the histopathological picture of the liver was observed in the group treated with CCl_4 plus mixture from ginger, aloe and citrus honey as the liver showed some cells have pyknotic nucleus, proliferation of van kupffer cells, vacuolar degeneration and nerobiotic changes of hepatocytes (Figure 4).

Figure (1): Microscopical examination of liver tissues of untreated control rat showing the normal histological structure (H and E. X 200).

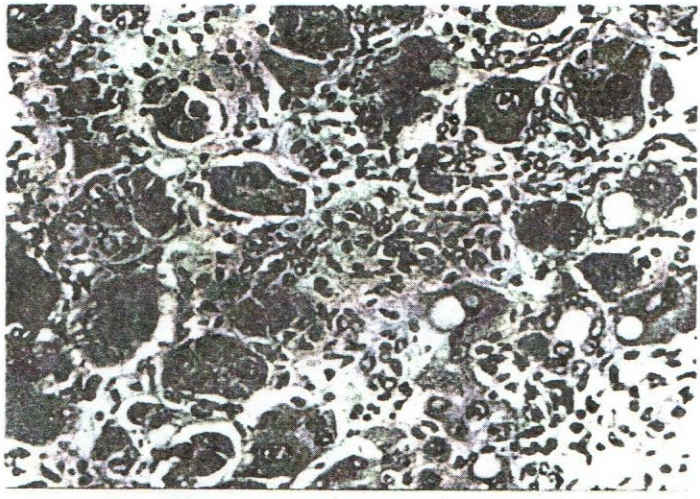

Figure (2): Microscopical examination of liver tissues of rats administered CCl_4 (3 ml/ kg b. w.) showing hepatocellular carcinoma with pleomorphic hepatocytes (H and E. X 400).

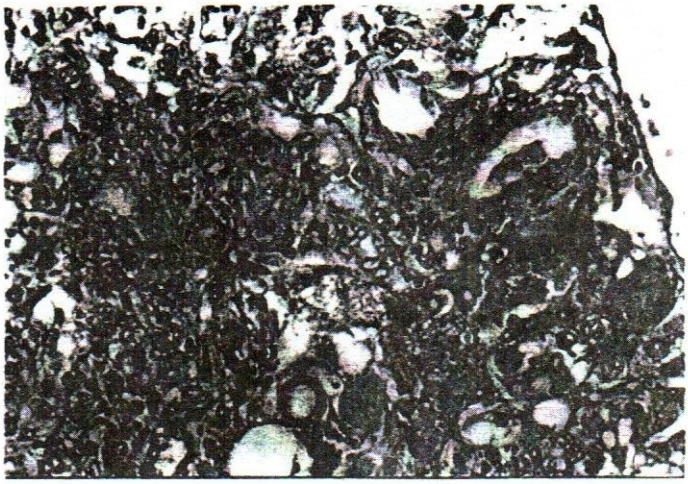

Figure (3): Microscopical of liver tissues of rats treated with CCl_4 plus ginger showing proliferation of bile duct lining cells, vacualar degeneration of some hepatocytes and necrosis of others (H and E, X 400).

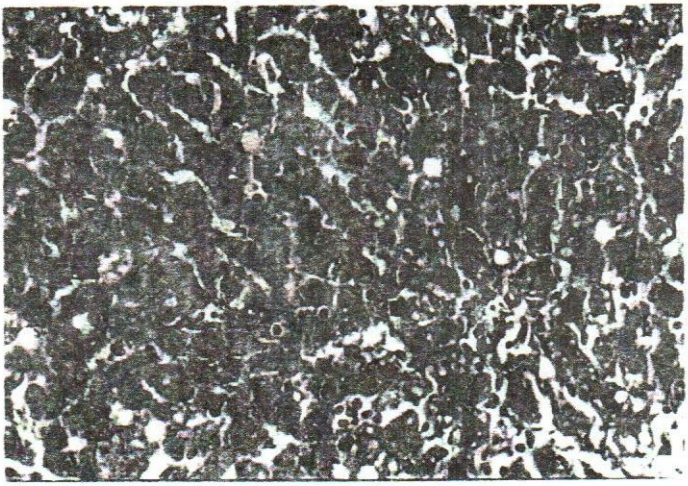

Figure (4): Microscopical of liver tissues of rats treated with CCl_4 plus mixture from ginger, aloe and citrus honey showing vacualar degeneration and necrobiotic changes of hepatocytes (H and E, X 400).

These results agreed quite well with the results of biochemical determination relevant to liver tests. It is clear that the mixture followed by ginger is more effective than bee honey and aloe for treatment hepatic carcinoma and chronic liver damage. These data are in agreement with those of Yoshimasa *et al.*, (2004) and Vaiyapuri and Namasivayam, (2005) who found that ginger has antioxidant and anticarcenogenic properties.

CCl_4 induced oxidative stress in many settings (Abraham *et al.*, 1999 and Das *et al.*, 2000). It is metabolized through the mitochondrial monooxygenase system. During metabolism, an unstable free radical, trichloromethyl, is rapidly converted to trichloromethyl peroxide (Recknagel *et al.*, 1989). Consequently, the cell membrane structure and membranes of intracellular organelles are totally damaged.

In conclusion, our results strongly suggest that oral administration of mixture from ginger, aloe and bee honey significantly inhibited liver cancer incidence, decreased circulatory lipid peroxidation and enhanced hepatocyte regeneration. It also improved the collagenolytic activity, the degradation of newly synthesized collagen and the repair of hepatocyte and enhance the recovery of liver fibrosis induced by CCl_4 in rats.

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التأثير العلاجي للزنجبيل والصبار وعسل النحل ومخلوطهم لمرض تليف الكبد المزمن والناشئ عن رابع كلوريد الكربون

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الهدف من هذه الدراسة هو تقييم فاعلية الزنجبيل والصبار وعسل النحل ومخلوطهم على التليف المزمن للكبد والناشئ عن التعرض لرابع كلوريد الكربون خلال ثمانية أسابيع . الفئران المصابة بتليف الكبد نتيجة المعاملة برابع كلوريد الكربون (٣ مللجم/ كجم من وزن الجسم) بالحقن في الغشاء البريتوني مرتين اسبوعيا ولمدة ثمانية أسابيع ثم معاملتها بالمواد المذكورة سابقا تحت الدراسة عن طريق الفم وبتركيزات ٠,١ جم ،٠,٥ جم ، ٣٤ جم والمخلوط بنفس النسب ، على التوالي ٥ مرات أسبوعيا ولمدة ثمانية أسابيع وتم سحب عينات الدم بعد ٢٤ ساعة ثم ٣ ، ٦، ٨ أسابيع . وتم تقدير بعض مكونات السيرم في هذه العينات مثل البليروبين الكلي والمباشر ونشاط الانزيمات الناقلة لمجموعة الأمين (ALT&AST) وانزيم الفوسفاتيز القاعدي (ALP) وفي نهاية التجربة تم تقدير الثيوباربتيوريك أسيد والكولاجين في الكبد . كما أجريت دراسات هستوباثولوجية لأنسجة الكبد لدراسة مدى تأثير هذه المواد في علاج تلف وتليف الكبد المزمن الذي أصاب هذه الفئران .

وأظهرت النتائج أن المعاملة برابع كلوريد الكربون أدى إلى إصابة الفئران بتليف نسيج الكبد وتكوين خلايا سرطانية مما أدى إلى ارتفاع مستوى نشاط الإنزيمات تحت الدراسة وكذلك البيليروبين والكولاجين وقيم TBA ولكن بعد المعاملة بالزعتر وجيل الصبار والعسل والمخلوط أدى إلى انخفاض ملحوظ في مستوى مكونات الدم والكبد السابقة الذكر لتقترب ألى الحالة الطبيعية وقد تم مقارنة النتائج مع ال silymarin المستخدم كعقار في علاج تليف الكبد وقد أظهرت الدراسة تفوق هذه المواد الطبيعية في العلاج على هذا العقار وقد أظهر المخلوط أعلى فاعلية في العالج يليه الزعتر . وأثبتت الدراسات الهستوباثولوجية لأنسجة الكبد أن للزعتر والمخلوط أثر علاجي ملحوظ وأن المخلوط كان أكثر فاعلية من الزعتر في وقف نمو الخلايا السرطانية وعلاج التليف وكانت بقية المعاملات أقل فاعلية.

لذلك توصي الدراسة بتناول جيل الصبار مع العسل والزنجبيل كغذاء يومي لعلاج الأورام الكبدية أو الوقاية من الإصابة بالتليف أو سرطان الكبد.