Journal of Pharmaceutical and Scientific Innovation
www.jpsionline.com
Research Article

HEPATOPROTECTIVE AND HEPATOCURATIVE EFFECTS OF NABK HONEY IN PENICILLIN-INDUCED HEPATIC TOXICITY

Ateeq M. J. Alarami[1]* and Mohammed S.A.Al-Awar[2]
[1]Department of Zoology, Faculty of Science, University of Thamar, Yemen
[2]Department of Biology, Faculty of Education, University of Amran, Yemen
*Corresponding Author Email: momed.sadeg@gmail.com
DOI: 10.7897/2277-4572.02571
Published by Moksha Publishing House. Website www.mokshaph.com

Received on: 09/08/13 Revised on: 26/09/13 Accepted on: 03/10/13

ABSTRACT
In our present research, we investigated the hepatoprotective and hepatocurative effects nabk honey in penicillin-induced hepatotoxicity. Biochemical analysis of serum was done for all groups. Hepatotoxicity was confirmed by comparing the serum levels of AST, ALT, ALP, total protein and albumin in penicillin-treated group with that of normal salinetreated groups. Nabk honey considerably ameliorated the toxic effects of penicillin on livers. Nabk honey showed the ability to avert the elevated serum AST, ALT and ALP levels, and augmented the total protein and albumin, along with improved histopathological changes in livers. On comparing between hepatoprotective and hepatocurative effects, hepatoprotective effect of nabk honey showed a considerably significant [$P < 0.01$] improvement in biochemical parameters and morphological changes of livers in penicillin-induced hepatotoxicity. Accordingly, hepatoprotective effect of nabk honey was more effective than hepatocurative effect of nabk honey.
Keywords: Hepatoprotective and hepatocurative, nabk honey, penicillin.

INTRODUCTION

Liver plays a major role in the detoxification and excretion of many endogenous and exogenous compounds; any type of injury (due to systemic drugs, food preservatives, agrochemicals and addiction to alcohol) or impairments of its functions may lead to many complications in one's health[1]. Antibiotics are widely used nowadays to cure many types ofdiseases[2]. Antibiotics have different courses ofadministration depending upon the seriousness of the infectionand the potency of the antibiotic taken. The recovery time of an individual may range from a week to a whole month[3]. One of the foremost concerns inmodern medicines is antibiotic resistance. Over the last decade, almost every kind of bacteria has become stronger and less responsive to antibiotic treatment when it is really required[4]. Although health benefits of antibiotics areoften emphasized, the side effects of antibiotics are notcommonly known[5]. Antibiotics are considered as a common cause of drug-induced liver injury (DILI)[6-8]. Penicillin antibiotics are bacteriostatic agents with abroad spectrum of antimicrobial activity. Besides their antimicrobialactivity, it has been shown that penicillin may be useful in the treatment of pathological conditions in whichacute or chronic inflammations are involved, such as dermatological, periodontal, rheumatic and neurodegenerative diseases[9]. Although the penicillin retains important roles in both human and veterinary medicines, the emergence of microbial resistance has limited their effectiveness[10]. Large doses of penicillinhave been shown to induce hepatic dysfunction in animal[11] and humans[12]. This dysfunction of the liver resulted in the disturbanceof nitrogen metabolism, jaundice and other signs of hepatocellulardamage, e.g., increase of serum transaminases. Al-Awar *et al.*[13] and Al-Shaibani *et al.*[14] observed a significant increase in the serum AST, ALT and ALP and a significant decrease in the serum total protein and albumin levels of guinea pigs treated with penicillin (50000 IU each/kg bw/day) for 30 days. Also Alqadhi[15] Akande *et al.*[16] recorded a significant increasein serum AST, ALT and ALP and a significant decrease in the serum total protein levels of rabbits treated with penicillin (10 mg/kg) for 10 days were also noted. Austin *et al.*[17] recorded a significant decreasein the albumin in the serum of mice after treatment with penicillin (10000 IU and 250000 IU/kg) for 21 days. The side effects which associate with the therapy by penicillin is mainly due the generation of an excessive amount of reactive oxygen species (ROS), resulting in the detrimental effects of the cellular antioxidant defense system, as well as, enhancement of the lipid peroxidation (LPO) process[18,19]. Reactive oxygen species (ROS) are an inevitable byproduct of cellular respiration causing oxidation of lipids, nucleic acids, and proteins. The (ROS) damage is an underlying cause of disease, including cancer, inflammatory, and neurodegenerative diseases[20-22], Liver disease[19]. Antioxidants protect key cell components from damage by neutralizing the free radicals[23]. Antioxidants that occur naturally in the body or are consumed through the diet may block damage to cells[24]. Therefore, supplementation of antioxidants can be considered as the alternative method to reduce such alterations. In fact, several studies demonstrated that the cellular antioxidant an activity is reinforced by the presence of dietary antioxidants[25]. Accordingly, interest has recently grown in the role of natural antioxidants used as a strategy to prevent oxidative damage as a factor in the pathophysiology of various health disorders[26]. Numerous of biological and pharmacological properties of honey have been noted, including antibacterial, antifungal, anti-inflammatory, antioxidant, immunomodulatory, antiviral and anti carcinogenic properties[27-30]. The mentioned properties of the honey are mainly due to the presence of many chemical compositions such as polyphenolic composites including flavonoids, tannins, terpenoids and phenolic compounds, that are known to have a free-radical scavenging activity and reduce the levels of ROS[31,32]. This study was designed to investigate the protective and curative effect of nabk honey to reduce the side effects induced by penicillin on some biochemical parameters as well as liver tissue structure.

MATERIALS AND METHODS

Chemicals

Penicillin (Procaine penicillin) in form white powder was obtained from (Ave Group-USA-Colombia-Mexico). Diagnostic kits for the aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein and albumin were obtained from Spinreact, S.A. Ctra. Santa Coloma, 7 E-17176 Sant Esteve DE Bas (GI) Spain.All other chemicals and reagents were of highest purity commercially available.

The honey used

The used honey (Nabk honey) was obtained from beekeeper, Mabian-Hajjah-Yemen.

Animals and experiment design

In this experiment 70 healthy Adult male guinea pigs, weighing 800 to 900 g, were obtained from the zoo, Sana'a-Yemen. Animals were housed in the animal house - Department of Biology- Faculty of Science- Sana'a University, under standard conditions in room temperature. Animals were allowed to acclimatize to the laboratory environment for 30 days. The animals were feeding fresh grass hay, alfalfais, legume, cabbage, carrot, celery and spinach as recommended by HCDGP[33] and GPCS[34] and tap water *ad libitum*. This experiment was divided into two parts:

Part 1

This part was mentioned to examine the protective effect of nabk honey on the Biochemical parameters (AST, ALT, ALP, total protein and albumin), in addition to their effect on the normal structure of liver tissues against the side effects of penicillin, for this goal, 40 guinea pigs were randomly divided into 4 groups as follows:-

Groups n = 10 guinea pigs	Dose / kg body weight	No. of Days / Route
Group-I Normal control	Normal saline Solution 5 ml/kg	For 30 days / Oral.
Group-2 Nabk honey control	Nabk honey 600 mg/kg	For 30 days / Oral.
Group-3 Penicillin Control	Penicillin 50000 IU/kg	For 30 days / Intraperitoneal injection (i.p).
Group-4 Nabk honey and Penicillin	Nabk honey 600 mg/kg and Penicillin 50000 IU/kg	For 30 days / Nabk honey / Oral and Penicillin / i.p.

Part 2

This part was mentioned to examine the curative effect of nabk honey on the mentioned in the part 1 parameters against the side effects of penicillin, for this goal, 30 guinea pigs were randomly divided into 3 groups as follows:-

Groups n = 10 guinea pigs	Dose / kg body weight	No. of Days / Route
Group-5 Normal control	normal slain Solution 5 ml/kg	For 40 days / Oral.
Group-6 Penicillin Control	Penicillin 50000 IU/kg for 20days + normal saline Solution 5 mg/kg for next 20 days	For 20 days / Penicillini. p. + normal saline Solution / Oral.
Group-6 Penicillin + Nabk honey for next	Penicillin 50000 IU/kg for 20 days + nabk honey 600 mg/kg for next 20 days	For 20 days / Penicillin / i.p.+ Nabk honey / Oral

The selected dose of Penicillin was based on previous studies[14,16], the selected dose of Nabk honey was according to Al-Awar *et al*.[13] and Gharzouli[35]. At the end of every part of experiment, guinea pig in all group were fasted overnight for 12 h and sacrificed under ether anesthesia, the blood was immediately collected and centrifuged and plasma was discarded and kept at - 21ºC for the biochemical tests. The liver of each guinea pig were removed, small pieces of liver were taken, then fixed by using a 10 % neutral formalin for 24 hours and were kept in alcohol for the tissue preparation.

Biochemical assay

Estimation of alanine- aminotransferase (ALT) and aspartateaminotransferase (AST)

The estimation was carried out according to the method originally developed by Reitman and Frankel[36].

Estimation of alkaline phosphatase

ALP was determined using a colorimetric method as described by Kind and King[37].

Estimation of total protein

The total protein was determined by Biuret method explained by Tietz[38].

Estimation of albumin

Serum albumin was determined according to the method of Doumas *et al*.[39].

Histological procedure

The liver of each guinea pig were removed. After the organs were removed, they were fixed by using a 10 % neutral formalin fixation for 24 hours. The fixed tissues were dehydrated in series of alcohol concentrations 70 %, 80 %, 90 % and 100 %. The dehydrated tissues were then cleared by using xylain as clearing agents. Then the cleared tissues were embedded in paraffin wax at 60°C. Blocks were cut at 5 mm thick and stained with hematoxylin and eosin[40].

Statistical analysis

The statistical analysis was performed by SPSS; continuous data are expressed as mean ± S.D. Data were compared using one – way ANOVA. P value <0.01 was considered to be statistically significant. post hoc analysis of grope differences was performed by LSD test. The treated groups were compared both with each other and with treated and untreated control groups.

RESULTS

Biochemical results

We measured biochemical parameters AST, ALT, ALP, total protein and albumin in order to determine the effect of nabk honey to reduce the toxic induced by penicillin. Group 2 animals which received penicillin (i.p) in a single dose 50000 IU/kg for 30 days showed significant rise in the levels of serum ALT, AST and ALP and significant fall in serum total protein and albumin as compared to control group (Table 1). Treatment with nabk honey alone in a single dose 600 ml/kg/day period of 30 day (group 3) showed comparable

results to the control regarding the AST, ALT, ALP, albumin and total protein (Table 1). Nabk honey has a protective and curative role against the side effects of penicillin in liver as demonstrated by the improvement in the tested biochemical parameters. Administration of honey to guinea pigs beside penicillin for 30 day highly significant decrease in AST, ALT and ALP and a significantly increase in total protein and albumin as to compared to penicillin treated group 2 (Table 1).

Table 1: Hepatoprotective effect of nabk honey on penicillin-induced changes in biochemical parameters

Groups N = 10	Treatment given	AST U/L	ALT U/L	ALP U/L	Total protein g/dl	Albumin g/dl
Group 1	Control. N.S for 30 days	21.95 ± 1.7	27.41 ± 1.8	52.91 ± 2.2	7.52 ± 0.28	3.78 ± 0.15
Group 2	Honey 600 mg/kg for 30 days	20.71 ± 1.9	27.33 ± 1.8	54.28 ± 1.8	7.69 ± 0.21	3.88 ± 0.22
Group 3	Penicillin 50000 IU/kg for 30 days	46.88 ± 4.9*	63.06 ± 5.6**	78.06 ± 4.3**	6.03 ± 0.45**	2.96 ± 0.18**
Group 4	Honey Penicillin 600 mg/kg + 50000 IU/kg for 30 days	24.58 ± 2.5$^{\#\#}$	30.71 ± 2.3$^{\#\#}$	55.33 ± 2.5$^{\#\#}$	7.38 ± 0.42$^{\#\#}$	3.68 ± 0.12$^{\#\#}$

The values are given as Mean ± Standard Deviation (M ± SD) (in each group); [$^{\#}$,* = Low significance; $^{\#\#}$, **= high significance] *P < 0.01, when compared with values of Control [Group1] N.S (Normal saline) #P < 0.01, when compared with values of penicillin Control [Group 3]

Group 6 animals which received penicillin (i.p) in a single dose 50000 IU/kg for 20 days showed significant rise in the levels of serum ALT, AST and ALP and significant fall in serum total protein and albumin as compared to control group (Table 2). Nabk honey has curative role against the side effects of penicillin in liver as demonstrated by the improvement in the tested biochemical parameters. Treatment with Honey for 20 days after withdrawal of penicillin therapy (group IV, 40th day) significantly reversed levels of AST, ALT, ALP, albumin and total protein as compared to penicillin treated group 6 (Table 2).

Table 2: Hepatocurative effect of Nabk honey on Penicillin-induced changes in Biochemical Parameters

Groups N=10	Treatment given	AST U/L	ALT U/L	ALP U/L	Total protein g/dl	Albumin g/dl
Group 5	Conrtol N.S for 40 days	22.76 ± 2.1	26.87 ± 2.5	53.45 ± 1.9	7.54 ± 0.43	3.90 ± 0.21
Group 6	Penicillin for 20 day + N.S for next 20 days	38.48 ± 5.8**	51.47 ± 4.1**	69.86 ± 4.9**	6.53 ± 0.67**	3.27 ± 0.31**
Group 7	Penicillin for 20 day + Honey for next 20 days	28.31 ± 3.7$^{*\#\#}$	35.43 ± 3.7$^{*\#\#}$	58.18 ± 2.5$^{*\#\#}$	6.96 ± 0.40$^{*\#\#}$	3.49 ± 0.28$^{*\#\#}$

The values are given as Mean ± Standard Deviation (M ± SD) (in each group); [$^{\#}$,* = Low significance; $^{\#\#}$, **= high significance]
*P < 0.01, when compared with values of Control [Group 5] N.S (Normal saline) #P < 0.01, when compared with values of penicillin Control [Group 6]

Histological results

Results in Figure 1, 6: The control livers show normal lobular architecture with central vein and radiating cords of hepatocytes, separated by blood sinusoids. Hepatocytes are large and polyhedral in shape with slightly acidophilic granular cytoplasm. They have large, rounded, vesicular nuclei with prominent nucleoli. Results in Figure 2: The liver cells of group 2 animals showed normal liver picture as in control group. Results in Figure 3, 4, 7: The liver cells of group 3, 6 animals showed obvious histological changes, in the form of distortion in the hepatic organization, dilatation and congestion of the blood sinusoids and central vein, infiltration, hemorrhage, congestion, inflammation, metaplasia, hyperplasia, hypertrophy, necrosis, vasodilatation, Some hepatocytes showed signs of degeneration in the form of hypertrophy with highly vacuolated cytoplasm and deeply stained nuclei. Other hepatocytes exhibited hyalinized cytoplasm with pale nuclei and prominent nucleoli. Results in Figure 5, 9: The liver cells of group 4, 8 appeared more or less similar to those of the control apart from few hepatocytes appeared with vacuolated cytoplasm and pyknotic nuclei.

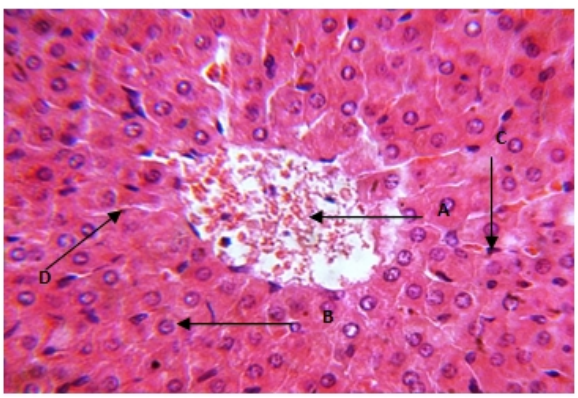

Figure 1. Light micrograph of a vertical section in the liver of guinea pigs after treatment with normal saline for 30 days, showing a normal architecturewithout pathological alterations. Spherical nucleus (B), Sinusoids (D), Blood vessel (A), and Kupffer cells(C). (HE) stain (X400).:

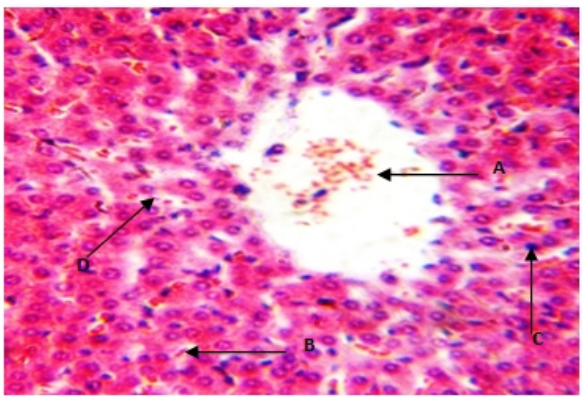

Figure 2. Light micrograph of a vertical section in the liver of guinea pigs after treatment with nabk honey for 30 days. showing a normal liver picture as in control group. Spherical nucleus (B), Sinusoids (D), Blood vessel (A), and Kupffer cells(C). (HE) stain (X400).

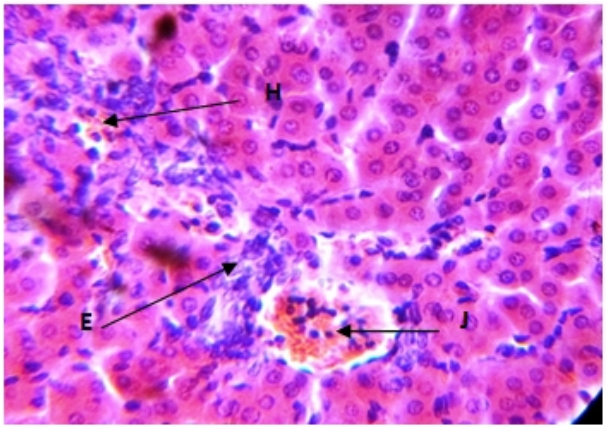

Figure 3. Light micrograph of a vertical section in the liver of guinea pigs after treatment with penicillin for 30 days. showing obvious histopathological changes. Hemorrhage (H), Congestion (J), Infiltration (E) . (HE) stain (X400).

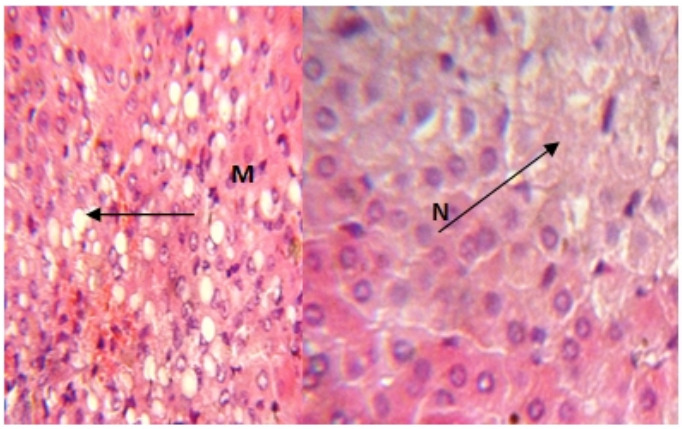

Figure 4. Light micrograph of a vertical section in the liver of guinea pigs after treatment with penicillin for 30 days. showing obvious histopathological changes. Odema (M), Necrosis (N). (HE) stain (X400).

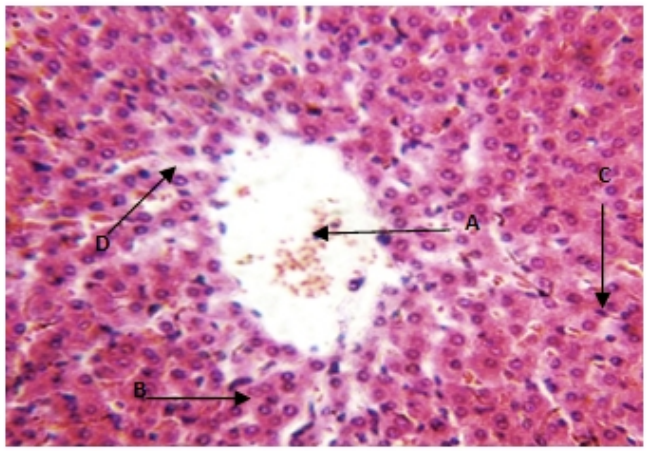

Figure 5. Light micrograph of a vertical section in the liver of guinea pigs after treatment with nabk honey and penicillin for 30 days. showing a normal liver picture as in control group. Spherical nucleus (B), Sinusoids (D), Blood vessel (A), and Kupffer cells (C). (HE) stain (X400).

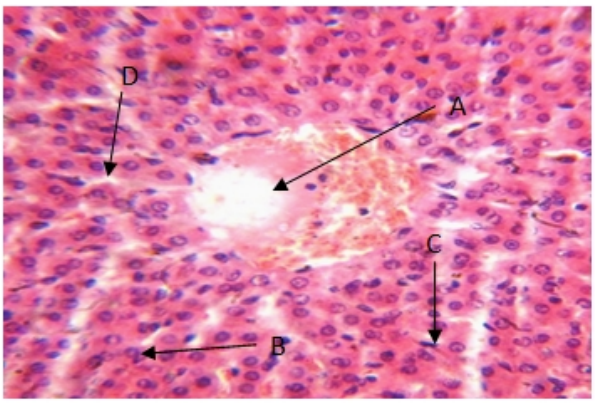

Figure 6. Light micrograph of a vertical section in the liver of guinea pigs after treatment with normal saline for 40 days., showing a normal architecturewithout pathological alterations. Sphericalnucleus (B), Sinusoids (D), Blood vessel (A), and Kupffer cells(C). (HE) stain (X400).:

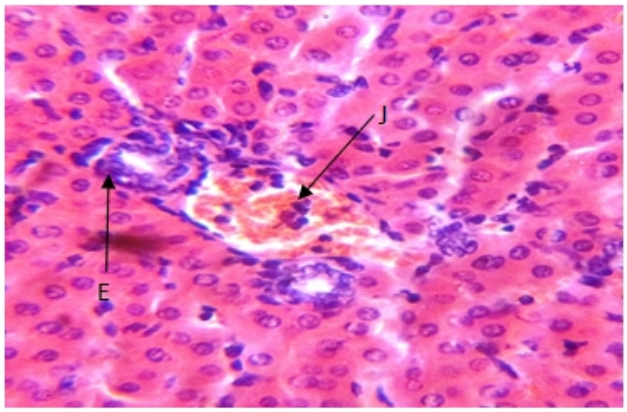

Figure 7. Light micrograph of a vertical section in the liver of guinea pigs after treatment Penicillin for 20days+ normal slain for next 20 days. showing obvious histopathological changes. Congestion (J), Infiltration (E) . (HE) stain (X400).

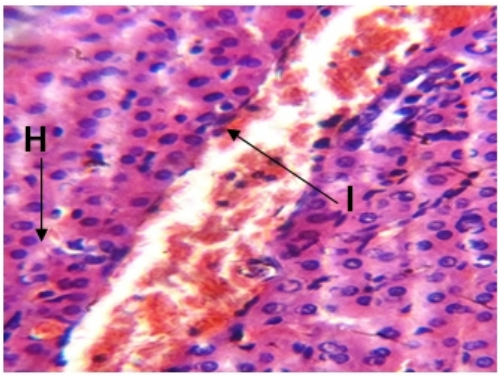

Figure 8. Light micrograph of a vertical section in the liver of guinea pigs after treatment Penicillin for 20days+ normal slain for next 20 days. showing obvious histopathological changes. Hemorrhage(H), Vasodilutation (I) . (HE) stain (X400).

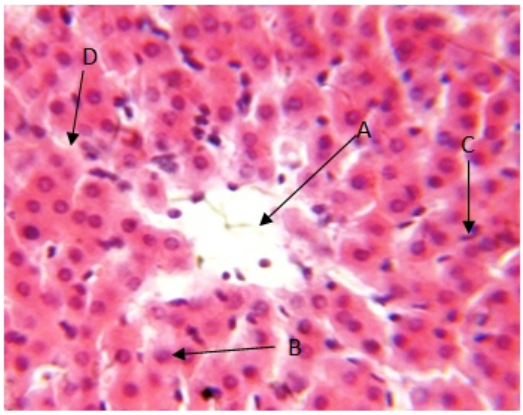

Figure 9. Light micrograph of a vertical section in the liver of guinea pigs after treatment Penicillin for 20days + nabk honey for next 20 days. showing a normal liver picture as in control group. Spherical nucleus (B), Sinusoids (D), Blood vessel (A), and Kupffer cells (C). (HE) stain (X400).

DISCUSSION

The noticed increase in the levels of aminotransferase (ALT and AST) and the level of ALP in the serum are the major diagnostic symptoms of liverdiseases[41]. In our study, Administering penicillin to guinea pigs resulted in a statistically highly significant increase the enzymes AST, ALT and ALP in the serum of the guinea pigs injected of penicillin only compared with the control group.These results may indicate to degenerative changes and hypofunction of liver[42-44] as well as hepatic cell necrosis[45] which increase the releasing of these enzymes in the blood stream[46]. Elevated levels of these enzymes in the serum are presumptive markers of drug-induced necrotic lesions in the hepatocytes[45]. The enhanced susceptibility of hepatocyte cell membrane to drug-induced peroxidative damage might have resulted in an increase releasing of these diagnostic marker enzymes into the systemic circulation. An increase in the AST and ALT levels indicates a reversible change of the cell membrane permeability[47]. Our observations are highly supported by the other studies which suggest effect penicillin on liver function tests[13-16]. In this study also, administering penicillin to guinea pigs resulted in a statistically highly significant decrease the level total protein and albumin in the serum of the guinea pigs injected of penicillin only compared with the control group. The reduction of total protein and albumin levels indicates that the administration of drugs has caused an impairment of liver function, e.g. its capacity to synthesize albumin from the hepatic parenchyma. Khan *et al*.[48] reported that there was a differential binding of penicillin with serum albumin, while Shen *et al*.[49] observed that albumin secretion of gel entrapped hepatocytes was reduced by penicillin. The decrement of alpha 1-globulin in the serum of penicillin-administrated animals could be due to liver dysfunction which affects the synthesis of alpha protein fractions in the liver. The increment of gamma-globulin level in the serum of tetracycline-treated animals may be due to hyperplasia of the reticulo-plasmic tissue of the bone marrow induced by penicillin Administration[50]. Our results are in agreement with[13,14,16,17]. The mechanism of penicillin-induced hepatotoxicity is found to be mediated through oxidative stress by free radical that cause damage to hepatocytes[51-53], AST, ALT and ALP increases in hepatic damage due to leakage of enzymes from damaged hepatocytes into vascular compartment. Liver damage leads to decrease in synthetic capability leading to fall in serum total protein and albumin levels[53]. Antioxidants can prevent cell damage due to the action of ROS and free radicals[54]. The antioxidant activities are related to a number of different mechanisms, such as free radical- scavenging, hydrogen-donation, singlet oxygen quenching, metal ion chelation, and acting as a substrate for radicals such as superoxide and hydroxyle[55]. Nabk honey has a protective and curative role against the side effects of penicillin in liver as demonstrated by the improvement in the tested biochemical parameters (AST, ALT, ALP, total protein and albumin). This indicates that nabk honey administration prevented liver damage by maintaining the integrity of the plasma membrane, thereby suppressing the leakage of enzymes through membranes, exhibiting hepatoprotective activity. This might be the main reason for the restoration in the activities of the marker enzymes during administration of honey oxidative damage in a cell or tissue which occurs when the concentration of ROS (O_2, H_2O_2 and OH) generated exceeds the antioxidant capability of free radical scavenger[57]. Previous reports demonstrated that nabk honey has a protective role against many toxicants drugs[13,32,56-59]. The present investigation clearly demonstrated that the injection of penicillin and antibiotics to guinea pigs have induced conspicuous alteration in the histological structure on the liver tissue in treated guinea pigs. These changes included dilatation and marked congestion of the hepatic vascularities (central veins, blood sinusoids and branches of the portal vein), cytoplasmic vacuolation, degeneration, infiltration, congestion, necrosis and karyolysis of hepatic cells as well as hyperplasia of endothelial; in addition, Infiltration, thickening in the central vein, metaplasia, hemorrhage, vasodilatation, hypertrophy and Odema. Our results are in agreement with[13,14.17] Histopathological changes in liver cells following injection of penicillin was the marked changes occurring in the liver in this study. This feature could be explained according the suggestion both of Tayala *et al*.[60]; Al-Awar *et al*.[13]; Al-Saibani[14] they reported that histopathological changes in liver cells due to free radical generating and free radical scavenging enzymes may be disturbed and leading to disrupt signal transduction pathway and increases the cellular permeability by acting on membrane phospholipids, resulting into a significant hepatic tissue injury . Dilatation and marker congestion of the hepatic vasculature of liver tissue which was noticed in the present investigation may be due the

failure of the heart which produces changes in different organs via two ways. Firstly, excessive blood in venous system increases blood pressure in the veins and capillaries which may exert undue pressure on the neighboring structures. Secondly, this is usually accompanied be a diminished blood supply, thus become subjected to malnutrition, deficient oxygenation and the accumulation of excretory and metabolic products[61]. Interpretation of vacuolar formation following chemical treatments has been subjected to wide speculation by many investigators. Robbins and Angell[62] regarded such vacuolation to represent primary morphologic response to many forms of cell injury. They also attributed it to the noxious effects of treatment on the cell membranes, both structurally and functionally, causing market disturbances in its permeability system. This presumably leads to enhanced imbibition of water into the cells. When it sufficiently accumulates in the cells, such intracellular water produced clear cytoplasmic vacuoles indication the occurrence of the pathologic symptoms commonly referred to as hydropic degeneration or fatty degeneration caused by lipid abundance in such instance. Other authors are of the opinion that cytoplasmic vacuolation is most probably brought about by the increase of lysosome elementsm[63]. The lysosomes contain hydrolytic enzymes, when these organelles are disrupted under certain pathological conditions: they liberate their powerful enzymes, which bring about considerable autolysis of various cellular parts[64]. Necrosis and degeneration of the hepatic cells following injection of penicillin was the marked changes occurring in the liver in this study. This feature could be explained according the suggestion of Curran[65] who reported that liver cells necrosis may be either due to progressive degenerative action of intracellular enzymes of the injured cells or to a metabolic disturbance and inhibition of synthesis needed of DNA and hence protein synthesis for the growth and maturation of the liver. On the other hand, the present histological study showed that of Nabk honey reduced the cellular changes induced by penicillin treated groups in both hepatoprotective and hepatocurative studies, indicating that Nabk honey contributed to the protection against penicillin induced liver toxicity. Our observations are highly supported by the other studies which suggest that Nabk honey exert their protective and curative effects against some drugs[59,66-](doxorubicin, penicillin, streptomycin, ibuprofen, acetaminophen and paracetamol)- induced hepatotoxicity[13,32,56-59,66]. On hypothesis to explain the beneficial effects of honey in ameliorating biochemical parameters and histological changes is that honey may contains flavonoids, ascorbic acid, tocopherols, catalase and phenolic compounds. All of which work together to provide a synergistic antioxidant effect, scavenging and eliminating free radicals[13].

CONCLUSION

In conclusion, we suggest that nabk honey may give beneficial results in the prevention of hepatic damage induced by the use of penicillin. On comparing between hepatoprotective and hepatocurative effects, hepatoprotective effect of Nabk honey showed a considerably significant [$P < 0.01$] improvement in biochemical parameters and morphological changes of livers in penicillin-induced hepatotoxicity. Accordingly, hepatoprotective effect of Nabk honey was more effective than hepatocurative effect of Nabk honey.

REFERENCES

1. Sapakal VD, Ghadge RV, Adnaik RS, Naikwade NS, Magdum CS. Comparative hepatoprotective activity of Liv-52 and livomyn against carbon tetrachloride induced hepatic injury in rats. Inter J Green Pharma 2008; 2: 79-82. http://dx.doi.org/10.4103/0973-8258.41175
2. Davey PG. Antimicrobial chemotherapy. In: Ledingham JGG, Warrell DA (Eds.), Concise Oxford Textbook of Medicine. Oxford University Press, Oxford; 2000. p. 1475.
3. Wiegand I, Hilpert K, Hancock RE. Agar and broth dilution methods to determine the minimal inhibitory concentration (MIC) of antimicrobial substances. Nat. Protoc 2008; 3(2): 163– 175. http://dx.doi.org/10.1038 /nprot.2007.521 PMid:18274517
4. Pearson C. Antibiotic Resistance fast-Growing Problem Worldwide. Voice of America http://voanews.com/english/archive/2007-02-28-voa33.cfm; 2008.
5. Koju D, Rao BS, Shrestha B, Shakya R, Makaju R. Occurrence of side effects from anti-tuberculosis drugs in urban Nepalese population under DOTS treatment. Kathmandu University. J. Sci. Eng. Technol 2005; 1(1).
6. Chalasani N, Fontana RJ, Bonkovsky HL. Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924–34. http://dx.doi.org/ 10.1053/j.gastro.2008.09.011 PMid:18955056 PMCid:PMC3654244
7. Andrade RJ, Lopez Ortega S, Lopez Vega MC. Idiosyncratic drug hepatotoxicity: a update. Expert Rev Clin Pharmacol 2008; 1: 261–76. http://dx.doi.org/10.1586/17512433.1.2.261
8. Robles M, Andrade RJ. Hepatotoxic dead pore antibiotics: actualization an [in Spanish (Hepatotoxicity by antibiotics: update in 2008); abstract in English]. Rev Esp Quimioter 2008; 21: 224–33. PMid:19031123
9. Miller EL. The penicillin: A review and Update. J. Mid and Women's Health 2008: 47(6): 426–434. http://dx.doi.org/10.1016/S1526-9523(02)00330-6
10. Young TE, Mangum B. The Antibiotics. Neofax: A Manual of Drugs Used in Neonatal Care, 20th ed.; Thomson Healthcare: Montvale. NJ. USA; 2007. p. 2-77.
11. Young DS. Effects of Drugs on Clinical Laboratory Tests. Third ed., vol. 3. AACC Press, Washington DC; 1999. p. 292–301.
12. Wruble LD, Cummins AJ. Tetracycline and fatty liver. Am. J. Dig. Dis 1965; 10: 742–744. http://dx.doi.org/10.1007/BF02236076 PMid:14316764
13. Al Awar MS, AL Shaibani EA, Salih EM, Al Eryanim MA. The Protective Effect of Nabk Honey against Pathological Effects of Penicillin and Streptomycin on Histological Structure and Functions of Guinea pigs Liver. J. App. Pharm. Sci 2013: 3(4 Supp 1): S1-S6.
14. AL Shaibani EA, Alarami AM, Al Awar MS, Salih EM, Al Eryani MA. Antioxidant protective effect of vitamin E in penicillin and streptomycin-induced hepatotoxicity in guinea pigs. J. Agricol. Bio. Sci 2013: 8(7): 546-554.
15. Alqadhi YA. The effect of the extreme and extreme use of Antibiotiotics on the immune indicatros and liver and Kidney Functions in experimental animals. Thesis M.Sc. Department of Biology. Faculty of Education Aden. University of Aden; 2013.
16. Akande T, Balogun ST, Gabriel O. The effects of penicillin streptomycin on liver aminotransferases, alkaline phosphatase and total serum protein in rabbits (Orcytolagusconiculus), J. Appli. Pharma. Sci 2012; 2: 32-35.
17. Austin H, Budowsky J, lane J, Chilton W. Reactions following to the use of penicillin. A controlled study. J. Aller 1993; 24 (2): 164 –171.
18. Westphal JF, Vetter D, Brogard JM. Hepatic side-effects of antibiotics. J Antimicrob Chemother 1994; 33: 387–401. http://dx.doi.org/10.1093 /jac/33.3.387 PMid:8040106
19. Andrade RI, Tulkens PM. Hepatic safety of antibiotics used in primary care. J. Anti microb. Chemother 2011; 17: 1-16.
20. Cadet J, Sage E, Douki T. Ultraviolet radiation mediated damage to cellular DNA. Mutation Research 2005; 571: 3–17. http://dx.doi .org/10.1016/j.mrfmmm.2004.09.012 PMid:15748634
21. De Flora S, Izzotti A. Mutagenesis and cardiovascular disease: Molecular mechanisms, risk factors, and protective factors. Mutation Research 2007; 621: 5–17. http://dx.doi.org/10.1016/j.mrfmmm. 2006.12.008 PMid:17383689
22. Brewer GJ. Iron and copper toxicity in diseases of aging, particularly atherosclerosis and Alzheimer's disease. Experimental Biology and Medicine 2007; 232: 323–335.
23. Dekkers JC, Van Doornen LJ, Kemper CG. The role of antioxidant vitamins and enzymes in the prevention of exercise-induced muscle damage. Sports Med 1996; 12: 213-238. http://dx.doi.org/10.2165/ 00007256-199621030-00005
24. Cherubini A, Vigna GB, Zuliani G Ruggiero, C Senin U and Fellin R. Role of antioxidants in atherosclerosis: epidemiological and clinical update. Curr Pharm Des 2011; 11: 2017-2032. http://dx.doi.org/10.2174/

1381612054065783
25. Prior RL, Cao G. Antioxidant phytochemicals in fruits and vegetables; diet and health implications. Hortic. Sci 2000; 35: 588–592.
26. Shireen KF, Pace RD, Mahboob M, Khan AT. Effects of dietary vitamin E, C and soybean oil supplementation on antioxidant enzyme activities in liver and muscles of rats. Food Chem. Toxicol 2008; 46: 3290–3294. http://dx.doi.org/10.1016/j.fct.2008.07.015 PMid:18706466
27. Ramos AF, Miranda JL. Honey: a review of its anti-inflammatory and healing actions. J. Venom Anim. Toxins incl. Trop. Dis 2007; 13(4): 679-710.
28. Jeffrey AE, Echazarreta CM. Medical uses of honey. Rev Biomed 1996; 7: 43-9.
29. Zaghlout AA, EL Shattawy HH, Kassem AA, Ibrahim EA, Reddy IK, Khan MA. Honey a prospective antibiotic extraction formulation and stability. Pharmazie 2001: 56: 643-647.
30. Abd El Ghany MA, Ramadan AM, Ghozy SF. Nutraceutical Effects of Curcuma, Ginger, Celery, Yeast and Honey on Side Effects of Gentamicin Induced Nephrotoxicity in Rats. World Appl. Sci. J 2012; 16(5): 646-655.
31. Gheldof N, Wang XH, Engeseth NJ. Identification and quantification of antioxidant components of honeys from various floral sources. J. Agric. Food. Chem 2002; 50: 5870-7. http://dx.doi.org/10.1021/jf0256135 PMid:12358452
32. Chandane RD, Jaju JB, Ghadlinge MS, Bhosale RR, Chandrakapure AR. Effect of honey on hepatotoxicity induced by antitubercular drugs in albino rats, Chandane *et al*. Int J Basic Clin Pharmacol 2013: 2(2): 177-181. http://dx.doi.org/10.5455/2319-2003.ijbcp20130311
33. Health Care and Diet for a Guinea pig. Lake Howell Animal Clinic; 2007. p. 526-534.
34. Guinea Pigs Care Sheet. Canyon Lake Veterinary Hospital; 2007.
35. Gharzouli K, Gharzoul A, Amira A and Khennouf S. Protective effect of mannitol, glucose-fructose-sucrose maltose mixture, and natural honey hyperosmolar solutions against ethanol-induced gastric mucosal damage in rats. Exper. Toxico. Pathology 2001; 53: 175-180. http://dx.doi.org/10.1078/0940-2993-00175 PMid:11484836
36. Reitman SS, Frankel SA. Colorimetric method for glutamic-pyruvate traansaminase, Am. J. Clin Path 1975; 28: 56-63.
37. Kind PR, King EG. Estimation of plasma phosphate by determination of hydrolyzed phenol with amino-antpyrine. J. Clin. Path 1954; 7: 56-63. http://dx.doi.org/10.1136/jcp.7.4.322
38. Tietz NW. Biuret method for the determination of total protein in serum. In: Fundamental of clinical chemistry. WBS Saunders Co. Philadelphia, Toronto, London, U.K; 1976. p. 503 and 879.
39. Doumas BT, Watson WA, Homer CB. Albumin standard and measurement of the albumin with bromocresol green. Clin Chem. Acta 1971; 31: 87-96. http://dx.doi.org/10.1016/0009-8981(71)90365-2
40. Humason GL. Animal tissue techniques. 2nd Edition. Freeman WH, and Company; 1979. p. 661.
41. Chatterjea MN, ShindeR. Text Book of Medical Biochemistry.6th ed. Jaypee Broth. New-Delhi; 2005. p. 644.
42. Kaplan MM. Primary biliary cirrhosis. N. Engl. J. Med 1987; 316(9): 521–8.http://dx.doi.org/10.1056/NEJM198702263160907 PMid:3543682
43. Abdel Wahhab A, Aly SE. Antioxidant property of *Nigella sativa* (black cumin) and *Syzygium aromaticum* (clove) in rats during aflatoxicosis. J. Appl. Toxicol 2005; 25(3): 218–23. http://dx.doi.org/10.1002/jat.1057 PMid:15856529
44. Adebajo AC, Iwalewa EO, Obuotor EM, Ibikunle GF, Omisore NO, Adewunmi CO. Pharmacological properties of the extract and some isolated compounds of Clausenalansium stem bark: anti-trichomonal, anti diabetic, anti-inflammatory, hepatoprotective and antioxidant effects. J. Ethnopharmacol 2009; 122(1): 10–9. http://dx.doi.org/10.1016/j.jep.2008.11.015 PMid:19095054
45. Singh VK, Dixit P, Saxena PN. Cybil induced hepato biochemical changes in wistar rats. J Environ Biol 2005; 26(4): 725–727. PMid:16459564
46. Jaramillo Jurez F, Rodrguez Vzquez ML, Rincn Snchez AR, Consolacin Martnez M, Ortiz GG, Llamas J. Acute renal failure induced by carbon tetrachloride in rats with hepatic cirrhosis. Ann Hepatol 2008; 7(4): 331–8.
47. Benjamin MN. Outline of veterinary Clinical Pathology. University press. Iowa; 1978. p. 229-232.
48. Khan MA, Muzammil S, Musarrat J. Differential binding of tetracyclines with serum albumin and induced structural alterations in drug-bound protein. Int. J. Biol. Macromol 2002; 30(5): 243–249. http://dx.doi.org/10.1016/S0141-8130(02)00038-7
49. Salih SB, Kharal M, Qahtani M, Dahneem L, Nohair S. Acute interstitial nephritis induced by intermittent use of rifampicin in patient with brucellosis. Saudi J. Kidney Dis. Transpl 2008; 19(3): 450–452. PMid:18445910
50. Mikaelian NP. Relationship of the reticulo – plasmocytic reaction of the bone marrow and serum hyper gamma globulinemia when tetracycline is administered to rabbits. Anti biotiki 1975; 20(1): 40–44. PMid:1122126
51. Parry MF. The penicillins. Med Clin North Am 1987; 71: 1093–112. PMid:3320613
52. Goldstein LI, Ishak KG. Hepatic injury associated with penicillin therapy. Arch Pathol 1974; 98: 114–7. PMid:4366005
53. Sherlock S, Dooley J. Drugs and Liver. In: Diseases of the Liver and Biliary System, 11th ed. Blackwell Science: Oxford, UK; Malden, MA; 2002. p. 335-63.
54. Cherubini A, Vigna GB, Zuliani G, Ruggiero C, Senin U, Fellin R. Role of antioxidants in atherosclerosis: epidemiological and clinical update. Curr Pharm Des 2005; 11: 2017-2032. http://dx.doi.org/10.2174/1381612054065783 PMid:15974956
55. Robards K, Prenzler PD, Tucker G, Swatsitang P, Glover W. Phenolic compounds and their role in oxidative processes in fruits. Food Chem 1999; 66: 401–36. http://dx.doi.org/10.1016/S0308-8146(99)00093-X
56. Garba AM, Mohammed B, Garba SH, Numan AI, Dalori BM. The effects of Honey and Aloe Vera extract on Ibuprofen Induced Liver Damage in rats.. J. Pharmac and Bio. Sci 2012; 3(2): 6-10.
57. Mahesh A, Shaheetha J, Thangadurai D, Rao DM. Protective effect of Indian honey on acetaminophen induced oxidative stress and liver toxicity in rat. Biologia 2009; 64: 1225–1231. http://dx.doi.org/10.2478/s11756-009-0205-5
58. Galal RM, Zaki HF, Seif El Nasr MM, Agha AM. Potential protective effect of honey against paracetamol-induced hepatotoxicity. Acade. Med. Sci of I.R 2012; 15(11): 674-680.
59. Ganash MA. Effect of honey histological changes in mice following exposure doxorubicin. J. Thesis M.Sc. Department of Biology. Faculty of Science. University of King Abdulaziz; 2005.
60. Tayala V, Kalraa BS, Agarwal SB, Khuran NA,Guptaa U. Hepatoprotective effect oftocopherol against isoniazid and rifampicin induced hepatotoxicity in albino rabbits. Ind. J. Exp. Biol 2007; 45: 1031-1036.
61. Haschek WM, Rousseaux CG. Hand book of toxicology pathology. Academic Press. London and New York; 1991.
62. Robbins SL, Angell M. Basic Pathology. 2nd ed. WB Saunders Company, Phildelphia, London; 1976.
63. Sorensen EM, Thomas P. Selenium accumulation reproductive status and histological change in environmentally expose dredger sunfish. Arch. Toxicol 1988; 61(4): 324-329. http://dx.doi.org/10.1007/BF00364858 PMid:3377688
64. El Banhawy MA, Sanad SM, Zahaby AS, Eid RM. An electron microscopic investigation on the effect one of the environmental pollutants on the mammalian liver. J. Egypt. Gar. Soc. Zool 1993; 12(C): 287-318.
65. Curran RC. Color atlas of histopathology. 3rd ed. Harvey Miller, London; 1985.
66. Ganash MA, Mujallid MI, Al Robai AA. The Possibility of Using Honey as Cytoprotective Against Pathological Effect of Doxorubicin Morphological Changes, Toxicological Symptoms, Histological Structure and Functions of Mice Liver. J. Unit of King Abdulaziz 2010; 21(2): 22-33.

Source of support: Nil, Conflict of interest: None Declared

QUICK RESPONSE CODE	ISSN (Online) : 2277 –4572
	Website http://www.jpsionline.com

How to cite this article:
Ateeq M. J. Alarami and Mohammed S.A.Al-Awar. Hepatoprotective and hepatocurative effects of Nabk honey in penicillin-induced hepatic toxicity. *J Pharm Sci Innov*. 2013; 2(5): 34-40.