



ISONIAZID (INH); HEPATOPROTECTIVE EFFECTS OF HONEY IN ISONIAZID (INH) INDUCED HEPATOTOXICITY IN RABBITS.

Umer Aleem¹, Rahman Shah², Noor Khan³ M. Suliman⁴

1. MBBS, M Phil (Pharmacology)
Assistant Professor
Department of Pharmacology
Saidu Medical College,
Saidu Sharif, Swat, Pakistan.
2. MBBS, M Phil (Pharmacology)
Assistant Professor
Department of Pharmacology
Swat Medical College,
Saidu Sharif, Swat, Pakistan.
3. MPH, PH.D (Public Health Scholar)
Research Supervisor
Saidu Teaching Hospital,
Saidu Sharif Swat.
4. BSc.N, MS
Lecturer
Khyber Medical University,
Peshawar.

Correspondence Address:

Dr. Noor Khan
Research Supervisor
Saidu Teaching Hospital,
Saidu Sharif Swat.
noorkhan193@hotmail.com

Article received on:

06/01/2018

Accepted for publication:

15/06/2018

Received after proof reading:

02/10/2018

ABSTRACT... Objectives: Hepatotoxicity is the most complicated side effect of isoniazid (inh) in the patient treated for tuberculosis. It causes 8–30% hepatotoxicity in the developing world. Metabolism of INH produces a metabolite, called acetyl isoniazid. In this study hepatoprotective effect of honey, in isoniazid induced animal model was assessed. **Study Design:** Randomized control trial. **Setting:** Saidu Medical College, Saidu Sharif Swat, KP. **Period:** October To December 2017. **Material and Methods:** 40 healthy male rabbits were assigned randomly to the group i, ii, iii and iv by using lottery method. Ten animals were grouped each row. The isoniazid-induced hepatotoxic model was created by giving 50 mg inh/kg orally on daily basis for eleven days. Group i was taken as negative control group ii as a positive control. Group iii and iv were experimental groups treated with 50 mg /kg/day and 100 mg /kg/day buckwheat honey respectively for eleven days. SPSS Version 16 software was used, mean, s.d. were determined in all the groups. Values of serum bilirubin, sgpt, and alkaline phosphatase were compared with each other using pair-test. **Results:** SGPT, Serum bilirubin, and alkaline phosphatase were obtained in all the animals. Comparing group 1 negative control with group 2, 3 and 4 shows statistical significance, (p=0.00). Comparing group 2 positive control with 3 and 4 shows statistical significance, (p=0.00). Further comparing group 3 with group 4 also shows statistical significance (p=0.00). **Conclusion:** From the above finding, it has been revealed that honey has got a protective effect in regressing hepatitis that has been induced in rabbit's model by high doses of isoniazid. Related studies performed in which different chemicals and drugs have been tried for their protective role in isoniazid induced hepatitis also shows a similar type of results.

Key words: Hepatotoxicity, Honey, LFTs, Isoniazid, Metabolism, Tuberculosis.

Article Citation: Aleem U, Shah R, Khan N, Suliman M. Isoniazid (INH); hepatoprotective effects of honey in isoniazid (INH) induced hepatotoxicity in rabbits.. Professional Med J 2018; 25(10):1587-1595. DOI:10.29309/TPMJ/18.4635

INTRODUCTION

The human body is composed of different biological systems that perform particular tasks necessary for everyday living things. This is because of the integrated functioning of different organs.

LIVER

Liver being a very important vital organ¹ performs numerous physiological functions. Liver weighing roughly 1.44-1.66 kg.² Liver lies in the abdomen below the ribs and consist of four lobes of different sizes Caudate and Quadrate.³ The liver is the largest glandular organ in the body and lies above the gallbladder.⁴ The liver performs various biological functions, among the important functions are⁵:

Synthesis

The liver is the site of synthesis for many biological molecules, including plasma proteins, clotting factors and also glucose from the breakdown of glycogen.⁶ Thrombopoietin is made primarily in the liver that regulates the production of platelets.⁷ If the liver is damaged or diseased, the corresponding synthesis is impaired and consequently, the respective function is altered.

Immunity

Liver is also capable of synthesis of immune factors, removes bacteria and prevents the body from infections. The liver is proposed as 'an immunological organ.'⁸ According to researchers' liver is an innate immune organ⁹, an immune organ¹⁰ and a lymphoid organ.^{11,12}

Metabolism

The liver also performs various metabolic functions, including metabolism of carbohydrates¹³, proteins, lipids and all other nutrients and drugs. Liver also converts ammonia into urea that excretes in urine.¹⁴

Storage

Liver stores glucose as glycogen to provide energy and also stores iron, fats, copper and a considerable amount of vitamins like vitamin A, D, K, and B.¹² Store of vitamins takes about 3 to 5 years to exhaust after stopping the intake of vitamins.¹⁵

Excretion

The liver plays an important role in the removal of body wastes, drugs, hormones and foreign substances. These substances are produced due to metabolism inside the body or in the form of foreign compounds and drugs from outside. The liver also converts some toxin to excrete in urine. Bilirubin which is a waste product excreted in bile.

Repair

One of the most interesting qualities of a liver is self-repair and damaged tissues regeneration.¹⁶ It is believed that 25% of the original liver mass can regenerate its full size.¹⁷ The liver becomes damaged when exposing to harmful substances while it clearing the body from these toxins. This shows that the self-repair capability is a significant property of the liver. Therefore if failing liver is supported for some time, regeneration occurs and the patient can survive and once again starts a normal life.

Though liver performs a lot of significant functions, still there is negligible specialization among hepatocytes. Excluding the macrophages in a liver that are called Kupffer cells, all hepatocytes are able to perform a wide variety of functions.¹⁸

HEPATOTOXICITY

As the liver transforming and clearing substances, therefore toxicity to these agents is common. Some drugs administered in overdoses or some other taken in therapeutics dose may cause hepatitis. Chemicals used in laboratories,

industries and herbal drugs also can cause hepatotoxicity. These substances are termed as hepatotoxins. About 900 drugs are responsible for liver damage.¹⁹ Some drugs cause sub-clinical liver injury and can be detected via Liver Function Tests (LFTs). About 5% admitted patients and 50% acute failures of liver are due to drugs.²⁰

Adverse drug reactions may be pharmacological, intrinsic or idiosyncratic. 80% drug reaction toxicities are intrinsic.²¹

Most of the drugs cause injury of mitochondria, which is enough for energy. Thus extreme dose of oxidants releases and causes liver damage. In cytochrome P-450 system the activation of some enzymes like CYP2E1, produce oxidative stress that leads to hepatic injury.²² After injury of liver and bile duct cells there is an accumulation of bile acids in the liver, that further increases the damage.²³ Fats storing cells, Kupffer cells and leucocytes also have some role in this mechanism.

Metabolism of the Drug in Liver

Human body identifies most of the drugs as foreign substances and makes them through chemical reactions to excrete easily by decreasing its fats solubility. Metabolism can occur in all body tissues but the liver worked as core organ for both exogenous and endogenous substances.²⁴ As liver is the main organ for metabolism, therefore, it can be affected more.

Transferases, Sulphate, Glutathione, Glucuronic Acid, Acetate and Cytochrome P-450 enzymes in liver, responsible for metabolism. Cytochrome P-450 is a group of about 50 isoforms, present in the endoplasmic reticulum (metabolic clearing house), all these enzymes metabolize more than 90% drugs.²⁵ Cytochrome P-450 system has three important properties in drug-induced toxicity. Liver Function Tests (LFTs): Serum alanine aminotransferase (ALT), serum bilirubin (SBR), and alkaline phosphatase levels (ALP) shows the degree of liver damage. Liver damage may be defined either;

- α. ALT level increases drastically above the double upper limit of normal (ULN) or

- β. ALP level increase above the double of the upper limit of normal (ULN) or
- χ. Total bilirubin level increases more than double of the upper limit of normal (ULN), along with increase in the ALT and ALP levels.²⁶

Liver damage may be hepatocellular when there is an increase level of ALT, or it might be cholestatic when the initial increase is in ALP level. However, utmost commonly there are mixed hepatic injuries. The drug-induced damage of liver may be due to damage of zonal necrosis, inflammation, granuloma, vascular lesions etc.

COMMON PHARMACOLOGICAL TOXINS

Acetaminophen

Frequently occurred causes of drug made liver disease are the overdose of acetaminophen. Usually, in prescribed doses, acetaminophen is not toxic but the overdosing is responsible for acute failure throughout the world.²⁷ Liver toxicity is not caused by the drug but due to metabolite "N-acetyl-p-benzoquinone imine (NAPQI)" that is hepatotoxic and create by cytochrome P-450 enzymes in the liver.²⁸ Normally this metabolite after conjugating in phase II reaction with glutathione, become detoxified. When heavy doses are taken there is increased production of (NAPQI) that overwhelms the process of detoxification and liver damage occurs.

Nonsteroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) though rarely cause liver damage but due to their widespread use they can cause hepatotoxicity. Some cases of hepatotoxicity by (NSAIDs) due to the unknown cause have been reported.²⁹ Intrinsic hepatotoxicity can cause by phenylbutazone and aspirin. Sulindac, ibuprofen, phenylbutazone, diclofenac, indomethacin, and piroxicam can cause an idiosyncratic reaction.

Glucocorticoids

Glucocorticoids stores glycogen in liver and long-term use of steroids can cause enlarged liver in children.³⁰

Isoniazid (INH)

The usual prescribing drug for tuberculosis is Isoniazid (INH). In 20% patients, liver enzymes increase with INH and in 1–2% causes hepatotoxicity.³¹ Monoamine oxidase inhibitors (MAOIs), which is hydrazine derivative, are responsible for hepatotoxicity.³² Natural products such as Amanita mushrooms, and ackee fruit such as camphor, cycasin etc,³³ are also hepatotoxic. INH hepatotoxicity is very common. There may be the asymptomatic increase in serum transaminases up to hepatic failure that needs transplantation. This type of hepatotoxicity caused not by increased plasma INH level but may be due to idiosyncratic response.³⁴

Hepatotoxicity due to INH is difficult to manage for several reasons. These patients may take any potentially hepatotoxic medications, with proper monitoring i.e. pyrazinamide, protease inhibitors. Therefore, it is not easy to find out the cause of the hepatic damage.

Hepatotoxicity due to INH is usually mild and it is not necessary to stop taking of drug but however, some patients develop severe hepatotoxicity that leads to failure of liver and death, if promptly the medications is not stopped due to non-availability of alternative effective drugs, INH is given continuously; though it can cause low grade hepatotoxicity. Severely affected patients may have few symptoms until gross liver damage has occurred.

Tuberculosis (TB)

Tuberculosis is the most common infectious disease and has remained the leading cause of death. The incidence of TB is different in different regions of the world. It is highest in South East countries of Asia region. Incidence of TB new patients and deaths from pulmonary TB is largest.³⁵ About 34% people throughout the world have been infected by mycobacterium tuberculosis. In 2007 the record shows that there were 13.7 million people suffering from active TB globally. The record of 2010 shows 8.8 million people developed T.B and 1.5 million people died from TB.³⁶

Tuberculosis (TB) is a disease which is more commonly caused by an infection with the bacteria mycobacterium tuberculosis. It is usually a disease of lungs but it also can affect any other organ of the body.

Experimental studies are in progress in which herbal products and synthetic chemical compounds are tested for their Hepatoprotective effects. Garlic, Silimaryn, N-Acetyl –Cysteine, Kaempferol and Metaltomine are said to have these effects.³⁷

According to Maryam et al 2010³⁷ Silimaryn antagonizes the action of Isoniazid in rabbit's model when concurrently given with isoniazid. The role of cytochrome 2E1 is also important in oxidative stress.

According to Tung-Yuan et al 2013³⁸ Kaempferol significantly reduces activity of CYP 2E1 however its effects on Isoniazid induced hepatotoxicity is not significant.

Similarly Paul et al 2006³⁹ showed hepatoprotective effect of garlic in animal model. Garlic has been shown to have antioxidants activity.

METHODOLOGY

Rabbits were kept in Saidu Medical College Swat's animal house. Each group was kept in a separate cage. Animals were kept at temperature of 22-24°C and humidity of 45-65 %. Natural light and dark cycle was available for their living. Water and food were supplied them accordingly.

ISONIAZID INDUCED HEPATOTOXIC MODEL

Isoniazid induced hepatotoxic model was created by giving 50 mg INH/kg orally on daily basis for eleven days. Isoniazid was obtained from Wyeth Pharma Lahore. This process was performed in the following manner.

Preparation of INH solution:

Stock Solution

To prepare stock solution, in 50 ml distilled water 500 mg INH was dissolved. Each ml. of stock solution having 10 mg INH. Each rabbit weighing 1 Kg was given 5cc of solution. According to

different weights, different CC of solution was given to different animals.

Procedure for Oral Intake

Ten CC syringes was taken. Needle was removed. NG tube was attached to the syringe. Drug solution was placed in the syringe. NG tube was passed through nose. Drug was given through nasogastric (NG) tube. As presented in Figure.5

Dosage Calculation of Honey for Each Group

Buckwheat honey was obtained from laboratories PCSIR Peshawar and was dissolved in normal saline.

- Group-I: In this group 5 cc/kg of 0.9% saline was administered to each animal for 11 days.
- Group-II: In this group INH 50 mg / kg /day /oral was administered for 11 days.
- Group-III: In this group INH 50 mg /kg/day/ oral was administered along with low dose honey. 50 mg /kg/day for 11 days. Honey was dissolved in normal saline that made up to 1 ml/kg solution.
- Group IV: In this group INH 50 mg /kg /day / oral was administered along with high dose honey 100 mg/kg/day. Honey was dissolved in normal saline and the solution was made up to 1 ml/kg.

Collection of Blood

After 11 days 2cc blood was drawn from vein in the edge of ear, of each animal, after application of xylol which has caused severe vasodilatation. As presented in Figure-1.



Figure-1: Collection of blood



Figure-2: Shifting of blood to gel tube

Blood was shifted to gel tube and was allowed to clot as shown in Figure-2.

It was placed in centrifuge machine for 10 minutes at the rate of 2500-3000 RPM (Rotation per minute).

Statistical Analysis

SPSS version 16 software was used for statistical purposes, value of n was 10 and distribution was normal in all cases. Mean, S.D. were determined in all the groups. Values of Serum Bilirubin, SGPT and Alkaline Phosphatase were compared with each other using pair-t test. P value < 0.05 is significant.

RESULTS

SGPT/ALT, Serum Bilirubin and Alkaline Phosphatase were obtained in all the animals.

Serum Bilirubin

In case of Group-I (Negative control) Serum Bilirubin minimum value was 0.56. Maximum value was 0.75. Mean value was 0.633.

In case of Group-II Serum Bilirubin minimum value was 0.32. Maximum value was 0.83. Mean value was 0.633.

In case of group-III Serum Bilirubin minimum value was 0.3. Maximum value was 0.9. Mean value was 0.55.

In case of Group-IV Serum Bilirubin, minimum

value was 0.65. Maximum value was 0.92. Mean value was 0.72.

Mean values of Group I, II, III and IV are presented in Table-I and Figures-3 & 4.

S. No	Group-1	Group-II	Group- III	Group-IV
1	0.62	0.83	0.9	0.92
2	0.75	0.82	0.8	0.90
3	0.58	0.75	0.8	0.82
4	0.63	0.70	0.6	0.75
5	0.57	0.65	0.6	0.70
6	0.71	0.60	0.4	0.4
7	0.59	0.55	0.7	0.4
8	0.63	0.45	0.4	0.65
9	0.68	0.32	0.3	0.3
10	0.56	0.66	0.68	0.68
Mean	0.633	0.633	0.55	0.724
S.D.	0.1607	0.1607	0.224	0.136

Table-I. Serum Bilirubin, in case of in Group-I (Negative Control), Group-II, Group-III & Group-IV.

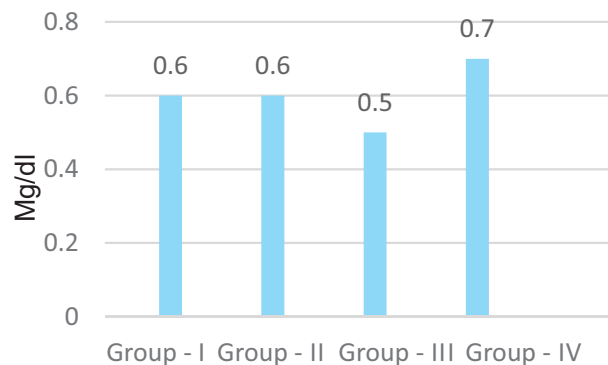


Figure-3. Serum Bilirubin

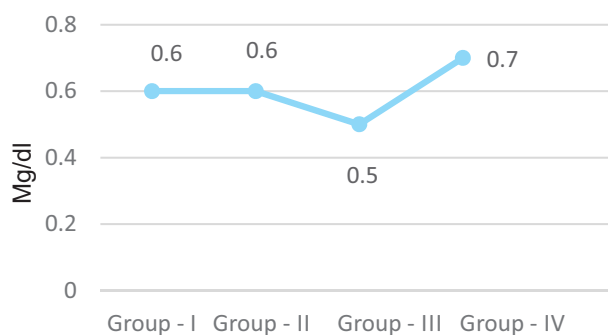


Figure-4. Serum Bilirubin

Alanine Amino Transferase (ALT/SGPT)

In case of Group1 (Negative control) the minimum value was 35.0. Maximum value was 47.6. Mean value was 41.49.

In case of Group-II SGPT, the minimum value was 170.4. Maximum value was 211.0. Mean value was 196.6.

In case of Group-III the minimum value was 132.1. Maximum value was 172.5. Mean value was 150.2.

In case of group IV the minimum value for SGPT was 122.3. Maximum value was 134.0. Mean value was 134.0.

Mean value of Group I, II, III and IV are presented in the Table-II and Figures-5 and 6.

S. No	Group 1	Group II	Group III	Group IV
1	36.2	188.2	140.7	132.2
2	42.3	206.5	153.4	128.4
3	38.6	202.8	160.4	136.4
4	46.9	170.4	136.4	127.2
5	42.3	192.7	172.5	122.3
6	35.0	189.1	158.4	139.1
7	39.9	208.0	163.4	141.2
8	41.2	211.1	132.1	150.0
9	44.4	196.1	141.0	126.7
10	41.6	196.8	150.3	134.0
Mean	41.49	196.6	150.2	134.0
S.D.	4.07	12.41	7.81	7.81

Table-II. ALT in case of Group-I (Negative Control), Group-II, Group-III & Group-IV

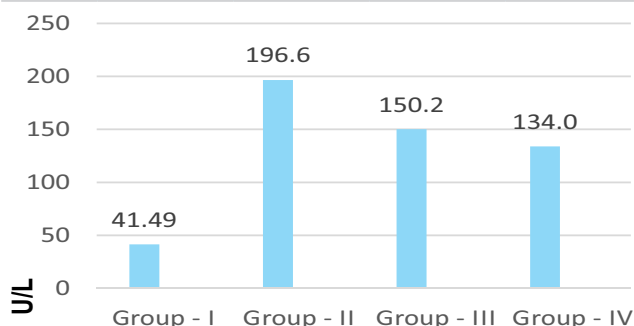


Figure-5. SGPT/ALT

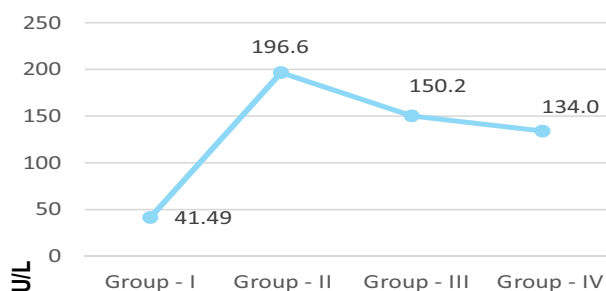


Figure-6. SGPT/ALT

Alkaline Phosphatase (ALP)

In case of negative control group minimum value for alkaline phosphatase was 98.0. Maximum value was 112.2. Mean value was 105.02.

In case of group II alkaline phosphatase, the minimum value was 104.1. Maximum value was 115.2. Mean value was 109.2.

In case of Group-III minimum value for alkaline phosphatase was 98.4. Maximum value was 106.2. Mean value was 102.08.

In group IV minimum value was 99.2. Maximum value was 107.2. Mean value was 103.08.

Mean value of Group I, II, III and IV are shown in Table-III and Figure-7 and 8.

S. No	Group-I	Group-II	Group-III	Group-IV
1	107.8	115.2	106.2	107.2
2	112.2	106.4	98.4	104.1
3	98.0	108.0	103.1	99.2
4	105.2	110.3	104.3	105.5
5	103.1	104.1	101.4	100.2
6	99.9	113.2	99.2	102.4
7	103.1	109.0	102.0	103.4
8	99.9	107.3	104.6	105.2
9	108.1	112.1	100.2	102.4
10	107.2	108.5	101.4	101.2
Mean	105.02	109.2	102.08	103.08
S.D.	4.46	3.34	2.48	2.50

Table-III. Values of Alkaline Phosphatase (ALP) in case of Group-I (Negative Control), Group-II, Group-III and Group-IV

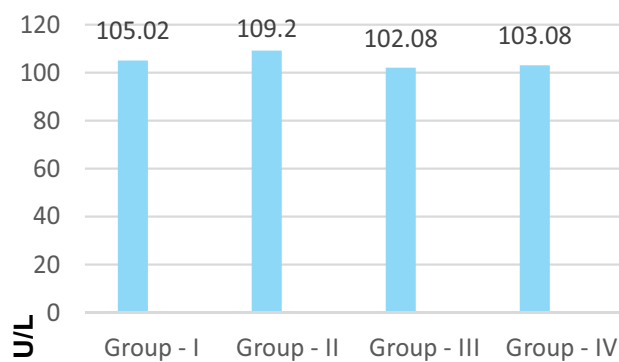


Figure-7. ALP

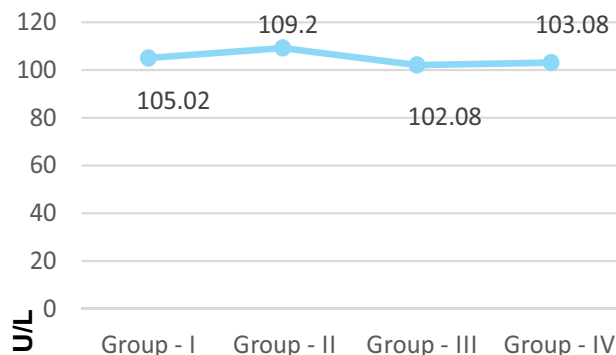


Figure-8. ALP

DISCUSSION

Most of the exogenous and endogenous compounds are detoxified and secreted by liver. Damage of hepatocytes may be due to viruses, systemic drugs, agrochemicals, alcohol, etc. Anti-tubercular drug also induces liver cell injury. Tuberculosis is a common disease, affecting people throughout the world. The common treatment regimen for tuberculosis (ATT) includes Isoniazid (INH), Rifampicin and Pyrazinamide. This is mediated through oxidative stress and free radical damage to hepatocytes.⁴⁰

Serum ALT increases in hepatic damage. ALT level also gives an idea of extent of damage caused to liver cells.

Honey is used in traditional medicine for centuries and has been used in different countries for reducing adverse effects of drugs. Most of the studies on honey show antioxidant property and Hepatoprotective effect.

In the present case the honey was used to see its protective effect in INH induced Hepatotoxicity in rabbits. The degree of the hepatotoxicity was assessed by Serum Bilirubin, serum ALT and serum ALP levels in different groups, medicated with 50mg and 100mg of honey for eleven days.

In case of SGPT/ALT in Group-I (Negative Control) the value of ALT was 41.4 ± 4.07 . In Group-II when INH was given the ALT value increased to 196.6 ± 12.41 . In Group III when 50 mg Honey was added, the ALT level decreased to 150.2 ± 7.81 . In group IV the dose of honey increased from 50

to 100 mg, it further decreased the ALT values to 134.0 ± 7.81 .

Comparing Group 1 negative control with group 2, 3 and 4 shows statistical significance ($P=0.00$). Comparing group 2 positive control with 3 and 4 shows statistical significance ($P=0.00$). This means that honey has regressing effect on INH induced hepatotoxicity. Further comparing group 3 with group 4 also shows statistical significance ($P=0.00$). That also shows the dose depend protective effect of honey on Isoniazid induce hepatotoxicity.

From the above finding it has been revealed that honey has got protective effect in regressing the hepatitis that has been induced in rabbits' model by high doses of Isoniazid.

This study revealed that honey has got protective effect in hepatotoxicity induced by isoniazid. However, randomized control trial should be performed to assess its value in human beings.

CONCLUSION

From the above finding, it has been revealed that honey has got a protective effect in regressing hepatitis that has been induced in rabbit's model by high doses of isoniazid. Related studies performed in which different chemicals and drugs have been tried for their protective role in isoniazid induced hepatitis also shows a similar type of results.

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*Listen without defending;
speak without offending.*

– Unknown –

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Umer Aleem	1st Author	
2	Rahman Shah	2nd Author	
3	Noor Khan	3rd Author	
4	M. Suliman	4th Author	