wjpmr, 2020,6(6), 295-301

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

MORINGA OLIFERA EXTRACT AS A HEPATOPROTECTIVE AGENT AGAINST RIMACTAZID-INDUCED HEPATOTOXICTY IN RATS

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Article Received on 21/04/2020 **Article Revised on 11/05/2020** **Article Accepted on 01/06/2020**

ABSTRACT

Hepatotoxicty, the most important problem worldwide gets the most attention from scientists as it considered a lethal disease. It arises as a side effect of many drugs, Alcohol abuse, liver malfunction and others. Rimactazid^{R} (Rim^{R}) is the first line drug for tuberculosis causes hepatotoxicity. Our study asses the hepatoprotective effect of *Moringa olifera* leaves water extract (MO) towards the hepatotoxicity induced by Rim^{R} in rats. Seventy – four rats (130-170g) were divided into 8 groups(7 rats for normal and drug groups and 10 rats for Moringa extract for each group). Co-administration of *Moringa oleifera* with Rim^{R} reduced the elevated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total protein, total bilirubin levels, malondialdehyde (MDA) and total antioxidant capacity (T.A.C). However, it elevated the reduced albumin. Hitopathological examination of MO extract groups showed the reduction in liver damage happened by Rim^{R} adminstration. From this study, we concluded that MO might be considered as hepatoprotective therapy with anti-tubercular drugs.

KEYWORDS: *Moringa olifera*; Hepatotoxicity; Rimactazid^{R}; *Mycobacterium tuberculosis*; malondialdehyde and Total antioxidant capacity.

INTRODUCTION

Tuberculosis (TB) is a deadly infectious disease that is caused by mycobacteria, mainly *Mycobacterium tuberculosis* and nearly infect one-third of the global population which caused death for 1.7 million in 2006 **Fingerote (2008)**. TB attacks most of the body organs mainly, the lungs as pulmonary TB **(Raviglione *et al.*, 1995)**.

Xiu-Hui *et al.* (2018) reported that the World Health Organization recommended Isoniazid (INH) and rifampicin (RMP) as the first-line antituberculosis drug. Although the using of antituberculosis drugs as isoniazid, rifampicin and additional antibiotic is accompanied by toxic reactions in tissues, especially in the liver which is leading to hepatitis **(Vinay *et al.*, 2013)** The ideal regimen for TB curing as documented by **Schaberg *et al.* (1996)** is by taking Isoniazid (INH), rifampicin (RIF), and pyrazinamide (PZA) for 8 weeks with a specific dose then only INH and RIF are completed for another 4-7 months in case the patient does not completely cured.

Guntupalli (2006) reported that liver disease is still considered a globally health problem particularly that are resulted from drug side effect, so most researches keen on studying the traditional herbal medicines especially that possess hepatoprotective activity and the method for using to deal with the severe undesirable side effects of synthetic drugs **(Manokaran *et al.*, 2008)**. Because of absence of any safe liver protective drugs, there is an urgent need for using herbal plants as they have significant role in handling with liver disorders as mentioned by **Pingale *et al.* (2008)**.

Moringa olifera is one of the most important herbal plants that is used in curing many diseases. It has anti-inflammatory effects, antihypertensive activity and analgesic (**Marugandan *et al.*, 2001; Dangi *et al.*, 2002; Kumari *et al.*, 2006)**. It also possess many biological activities as antidiabetic and hypocholesterolemic **(Mehta *et al.*, 2003; Kar *et al.*, 2003; Broadhurst *et al.*, 2000)** and many other diseases such as hepatoprotective against antitubercular drug such as isoniazid and rifampicin **(Pari and Kumar, 2002; Fakurazi *et al.*, 2008)**.

A lot of studies held on *M. olifera* extract proved that the treatment with it or with its isolated phytochemical can

make detoxification by elevating the antioxidant enzyme **(Faizi *et al*., 1994; Rao *et al*., 1999; Fahey *et al*., 2004)**. The incorporation between the phytochemicals and antioxidant enzymes found in Moringa in addition to its nutritive value may be enough to make more exertion on the prevention of oxidative stress that is induced by TB drugs. Additionally, the Moringa has free radical scavenging and antioxidant activities as reported by **Santos *et al.* (2005)**. The objective of this study is to investigate the protective and therapeutic role of *Moringa olifera* against the induced- Rimactazid^{R} hepatotoxicity.

MATERIAL AND METHOD

Drugs

Rimactazid 300 coated tablets: Each tablet contains 300mg rifampicin and 150 mg isoniazid. Drug was purchased from the local market as a tablet form manufactured by Sanofi aventis. Co, Cairo; Egypt under the license from Gruppo Leptit S.R.L. Italy.

Plant Collection and Extraction

Dried leaves of *Moringa oleifera* Lam. (Moringa) was used in the experiment. The dried powdered leaves was boiled with distilled water (1:10, w/v) at 100◦C for 30 min and then filtered. The boiled leaves were re-extracted until exhaustion. The concentration of extract was adjusted to prepare two different doses introduced to rats used in the experiment, low dose of 200 mg/kg bwt and high dose of 1600mg/kg bwt.

Animals

Eighty-eight adult male albino rats weighing 100-120 g were used in the experiment. They were obtained from the animal house of National Organization of Drug Control and Research, (NODCAR), Cairo, Egypt. All animals were maintained on a standard diet containing: Crushed wheat (46%) shredded barley (40%), fishmeal powder (9%), dried milk (3%), yeast (1%), minerals and vitamins (1%). Animals were housed 6 per cage and were kept in air-conditioned room (temperature 25±1◦C). Food and drinking water were available ad libitum during the entire experimental periods.

Study Design

Experimental animals were treated for 8 weeks according to the experimental design. They were classified into eight groups as shown in table (1).

Table 1: Classification of rat groups for experimental design.

Group code	No. of rats	Type of treatment
NG	7	without treatment (Saline only)
DG	7	treated with Rim^{R} for 8 weeks
MG1	10	200 mg/kg bwt MO + Rim^{R}
MG2	10	200 mg/kg bwt MO for 4 weeks then Rim^{R} for 4 weeks
MG3	10	Rim^{R} for 4 weeks then 200/kg bwt mg MO for 4 weeks
MG4	10	1600 mg/kg bwt MO + Rim^{R} for 8 weeks
MG5	10	1600 mg MO for 4 weeks then Rim^{R} for 4 weeks
MG6	10	Rim^{R} for 4 weeks then 1600 mg/kg bwt MO for 4 weeks

Rim^{R}: Rimactazid; Mo:Moringa Olifera extract, NG; Negative control, rats received saline ; DG: positive control, rats received drug; MG(1-6): Moring group, rats received MO+Rim^{R} with different administration method and doses.

Blood samples were collected from all the experimental animals after 24 h of the last administration. AST, ALT, GGT, total billirubin, albumin, total antioxidant, MDA, alkaline phosphatase and total protein were analyzed.

Biochemical investigations

AST, ALT and GGT were determined using **Chen, Tsai *et al.* (2017)** methods. Alkaline Phosphate (ALP) was determined as outlined by **Beifield and Goldberg (1971)**, total bilirubin was determined according to **Walter and Gerade (1970)**, total protein was determined according to **Gornal *et al.* (1949)** and albumin was determined according to **Doumas *et al.* (1971)**. The liver content of MDA was determined according to **Satoh (1978)** and its total antioxidant capacity (T.A.C) was determined according to **Koracevic *et al.* (2001)**, using Biodiagnostic kits, Egypt.

Liver histopathological assessment

Liver tissue specimens were fixed in 10% formol saline, then trimmed off, washed and dehydrated in ascending grades of alcohol. The dehydrated specimens were then cleared in xylene, embedded in paraffin blocks and sectioned at 4-6 µm thick. The obtained tissue sections were deparaffinized using xylol and stained using hematoxylin and eosin (H&E) for histopathological examination through the electric light microscope according to **Bancroft *et al.* (2013)**.

Statistical Analysis

All results were expressed as mean ± SD for each group. Data was analyzed with student's t-test using SPSS version 25. P values ≤ 0.05 were considered significant.

RESULTS

1- Effect of the drug on levels of serum liver enzymes

The present results showed that the hepatotoxicity is induced through elevating serum levels of ALT, AST,GGT, ALP, total protein, total bilirubin and reduction in albumin level by 4.66,6.93, 4.17,1.1, 1.16, 2.88, 0.6 times, respectively (Fig 1,2,3), when compared to NG. (Table 2)

2- Effect of the drug on the oxidative stress in liver:

The biochemical results revealed that induction of hepatotoxicity by drug elevated the liver content of MDA and the (T.A.C) by 4.29 and 4 times, respectively (Fig. 3), as compared to NG. (Table 3)

3- Effect of co-administration of extract in MG 1, 2 and 3 on the levels of serum liver enzymes:

The treatment with MO extract in MG 1, 2 & 3 significantly reduced serum levels of ALT by 1.56, 3.94 and 3.94 times, respectively, AST by 4.08, 3.13 and 2.21times, respectively, GGT by 4.30, 5.44 and 1.33 times, respectively, ALP by 1.05, 1.22 and 1.24 times, respectively, total protein by 1.13, 1.08 and 1.5 times respectively, total bilirubin by 1.64, 2.3 and 1.53 times, respectively and elevated the albumin level by 1.34, 1.28 and 1.03 times, respectively (Fig 1,2,3), when compared to DG. (Table 2)

4- Effect of co-administration of extract in MG1, 2 and 3 on the oxidative stress in liver:

The treatment with MO extract in MG1,2 and 3 significantly reduced liver content of MDA by 2.29,1.93 and 2.07 times, respectively and the (T.A.C) also reduced by 1.88,1.88 and 1.88 times, respectively (Fig,3), when compared to DG. (Table 3)

5- Effect of co-administration of extract in MG 4, 5 and 6 on levels of serum liver enzymes:

The treatment with MO extract in MG 4, 5 and 6 significantly reduced serum levels of ALT by 3.14, 2.8 and 3.95 times, respectively, AST by 2.12, 1.66 and 1.68 times, respectively, GGT by 5.55, 4.17 and 4.14 times, respectively, ALP by 1.07, 1.08 and 0.94, times respectively, total protein by 1.18, 1.21 and 1.15 times, respectively, total bilirubin by 2.56, 3.29 and 2.86 times, respectively and elevated the albumin level by 1.31, 1.59 and 1.59 times, respectively (Fig. 3), when compared to DG. (Table 2)

1- Effect of co-administration of extract in MG 4, 5 and 6 on the oxidative stress in liver:

The treatment with MO extract in MG 4, 5 and 6 significantly reduced liver content of MDA by 3.01, 4.44 and 3.98 times, respectively and the (T.A.C) also reduced by 2.9, 4.57 and 3.56 times respectively, when compared to DG. (Table 3)

2- Effects of *Moringa oleifera* extract on liver histopathology:

The treatment with MO extract effects on the liver histopathology as shown in Fig.4 (A-H): Histopathology of rat liver showing (A) normal morphology with preserved hepatic architecture of NG; (B) focal necrotic foci and hydropic degeneration of hepatocytes. Few number micro-vesicular steatosis and apoptotic bodies were seen in DG; (C) normal arrangement of hepatic cords. The hepatocytes revealed hydropic degeneration and hyperplasia of Kupffer cells score I. Few number of leukocytic infiltration was seen in-between hepatic cells.in MG1; (D) hydropic degeneration of hepatocytes and narrowing of sinusoids score I**.** Hyperplasia of Kupffer cells and few number of lymphocytic infiltration were seen in MG2; (E) hydropic degeneration and necrosis score III**.** Hyperplasia of Kupffer cells and Few number of lymphocytic infiltration were seen in MG3; (F) The hepatocytes of hepatic lobules showed mild swelling and granularity of its cytoplasm score I in MG4; (G) normal hepatic lobules which are made up of cords of polygonal cells with prominent round nuclei and eosinophilic cytoplasm like control group score 0 in MG5; (H)The hepatic lobules showed marked hydropic degeneration of hepatocytes and narrowing of its sinusoids score I. Hyperplasia of Kupffer cells was seen in MG6.

Table 2: Effects of *Moringa oleifera* extract on serum liver enzymes.

Moringa extract conc.		**Treated with 200 mg Moringa**			**Treated with 1600 mg Moringa**			
Analysis type	NG	MG1	MG2	MG3	MG4	MG5	MG6	DG
GPT	3.3±0.2	9.9±2.1 [ab]	3.9±0.8 [ab]	3.9±0.7 [ab]	4.9±1.07 [ab]	5.5±1.06 [ab]	3.9±0.5 [ab]	15.4±3.5 [a]
GOT	7.0±0.3	11.9±2.8 [ab]	15.5±3.5 [ab]	21.9±2 [ab]	22.9±3.7 [ab]	29.2±6.3 [ab]	28.9±5.9 [ab]	48.5±5.1 [a]
GGT	13.3±1.7	12.9±1.4 [ab]	10.2±1.2 [ab]	41.6±4.9 [ab]	10 ±0.9 [ab]	13.3±2.1 [ab]	13.4±1.8 [ab]	55.5±5.4 [a]
ALP	76.4±11.3	80.1±4.4 [ab]	69.3±3.9 [ab]	68.1±5.8 [ab]	78.9±4.9 [ab]	77.7±7.8 [ab]	89.8±8.4 [ab]	84.3±3.5 [a]
Albumin	4.8±0.1	3.9±0.5 [ab]	3.7±0.2 [ab]	3.0±0.2 [ab]	3.8±0.1 [ab]	4.6±0.3 [ab]	4.6±0.3 [ab]	2.9±0.15 [a]
Total Protein	7.3±1.0	7.5±0.7 [ab]	7.9±0.6 [ab]	8.1±0.4 [ab]	7.2±0.6 [ab]	7.0±0.9 [ab]	7.4±0.9 [ab]	8.5±0.1 [a]
Total Bilirubin	0.8±0.1	1.4±0.6 [ab]	1.0±0.2 [ab]	1.5±0.2 [ab]	0.9±0.1 [ab]	0.7±0.1 [ab]	0.8±0.1 [ab]	2.3±0.4 [a]

** Data are shown as mean ± SD*

a: Different significantly against negative control

b: Different significantly against positive control

Table 3: Effects of *Moringa oleifera* extract on oxidative stress.

Moringa extract conc.		Treated with 200 mg Moringa			Treated with 1600 mg Moringa			
Analysis	NG	MG1	MG2	MG3	MG4	MG5	MG6	DG
T.A.C	0.8±0.2	1.7±0.4^{ab}	1.7±0.6^{ab}	1.7±0.4^{ab}	1.1±0.1^{ab}	0.7±0.2^{ab}	0.9±0.2^{ab}	3.2±0.4^{a}
MDA	99.3±17.8	185.5±14.9^{ab}	220.9±21.2^{ab}	205.7±24.9^{ab}	141.3±16.2^{ab}	96±9.8 ^{ab}	106.9±17.4 ^{ab}	425.9±35.4^{a}

** Data are shown as mean ± SD*
a: Different significantly against negative control
b: Different significantly against positive control

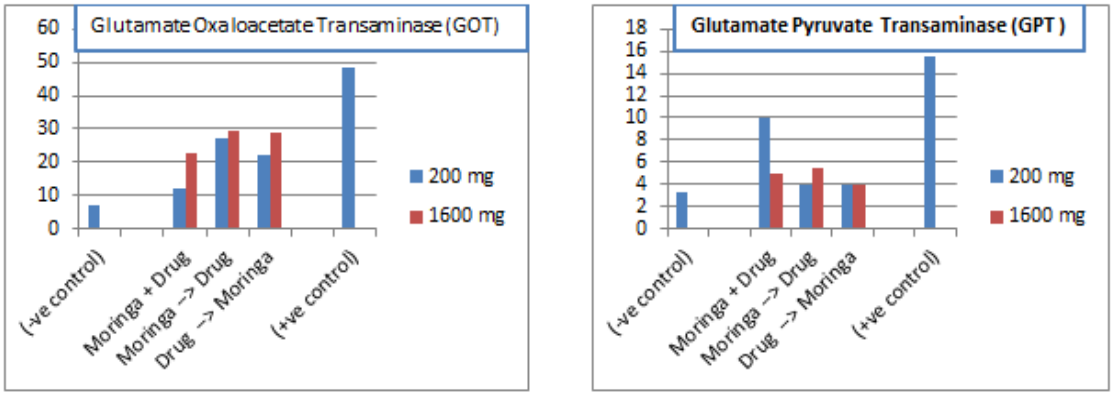

Fig. 1: Effects of *Moringa oleifera* extract on GPT and GOT enzyme activities.

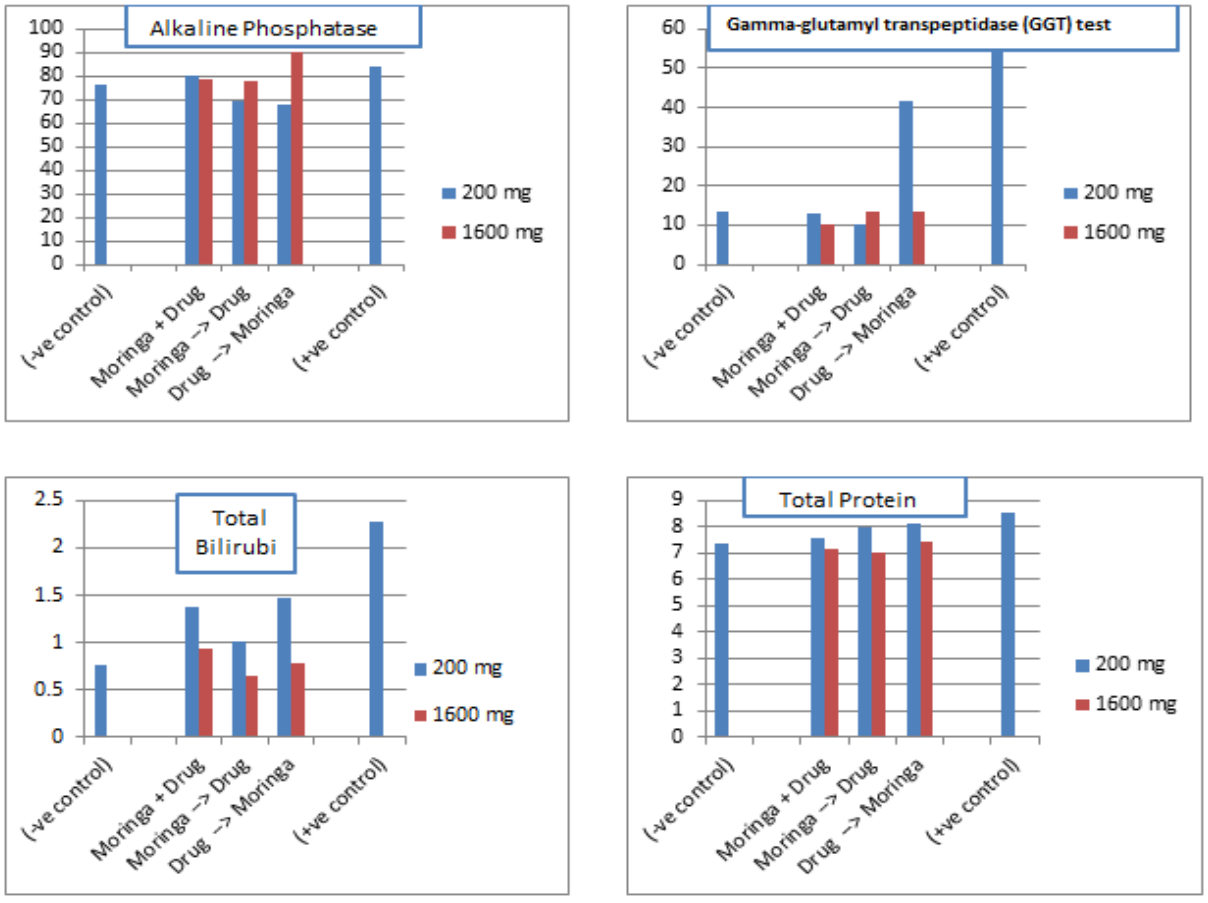

Fig. 2: Effects of *Moringa oleifera* extract on GGT, ALP, total bilirubin and total protein.

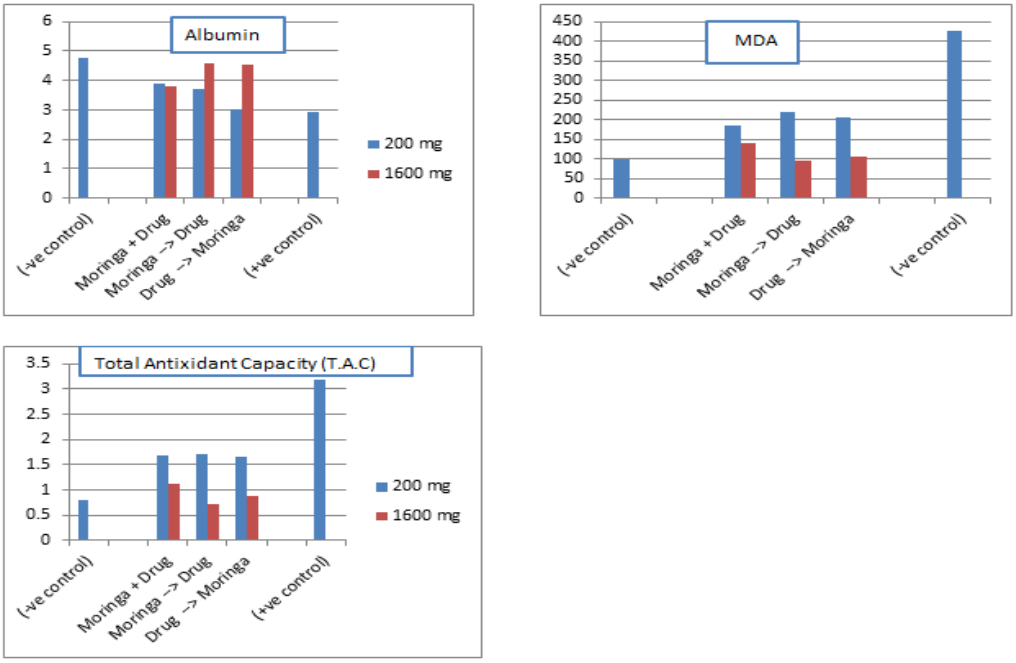

Fig. 3: Effects of *Moringa oleifera* extract on albumin and oxidative stress.

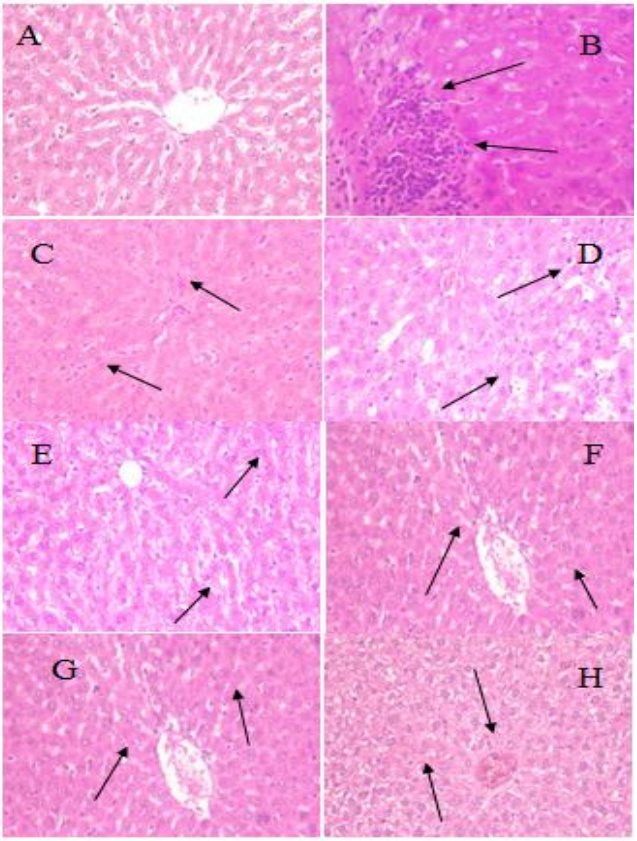

Fig. 4: Effects of *Moringa oleifera* extract on liver histopathology.(Fig. A Hepatic tissue section showing normal histological structure of hepatic lobules (H&E x 200) Fig. B Hepatic tissue section showing disorganization of hepatic cords and necrobiotic changes of hepatocytes arrow (H&E x 200) Fig. C Hepatic tissue section showing granular degeneration of hepatocytes arrow (H&E x 200) Fig. D Hepatic tissue section showing hydropic degeneration and vacuolation of hepatocytes (H&E x 200) Fig. E Hepatic tissue section showing disorganization of hepatic cords and necrobiotic changes of hepatocytes (H&E x 200) Fig. F Hepatic tissue section showing normal hepatic lobules with mild swelling of hepatocytes arrow (H&E x 200) Fig. G Hepatic tissue section showing normal hepatic lobules with mild swelling of hepatocytes arrow (H&E x 200) Fig. H Hepatic tissue section showing marked hydropic degeneration of hepatocytes arrow (H&E x 200).

DISCUSSION

The liver enzymes (AST, ALT and GGT activities) for the group treated with Rimactazid^{R} (+ve control group) were significantly increased compared to normal control group. The elevation in the activity of liver enzymes is considered as the toxic side effect of the drug as mentioned by **Eminzade *et al.* (2008)**. A significant decrease was also observed in the liver enzymes for the high dose of Moringa extract than that of the low dose when they compared to drug group. This means that the extract could decrease the induced hepatotoxicity induced by the drug. This result was in agreement with **Salama *et al.* (2018)**. The hepatotoxicity induced by drug group was clearly revealed by second increase in the biochemical markers ALP activity and total bilirubin level compared to control as well as the Moringa extract groups where the results for high dose is better than that of low dose. These results were in agreement with **Bello *et al.* (2012) and Qader *et al.* (2014)**. These elevations are because of their excess leakage from degenerated hepatocytes and the lockage of bile canaliculi as a result of inflammatory cells infiltration **(Tasduq *et al.*, 2007)**. Additionally, third elevation in the total protein level of drug administrated rats was noticed compared to both normal group and Moringa extract groups where the results for high dose is better than that of low dose, this elevation is also indication to the liver toxicity induced by the drug as showed by **Jemikalajah *et al.* (2014)**.

On the other hand, there is a significant decrease in serum albumin level for drug group compared to normal group (Moringa extract groups) where the results for high dose is better than that of low dose, due to the alteration in the protein and free amino acid metabolism and their synthesis in the injured hepatocytes as reported by **Eminzade *et al.* (2008)**.

It is known that Rimactazid^{R} causes hepatotoxicity by increasing the oxidative stress and lipid peroxidation which finally leading to liver damage (**Attri *et al.*, 2000; Richards *et al.*, 2004**). The malondialdehyde (MDA) which is a product of lipid peroxidation, and the total antioxidant levels were measured in the hepatic tissues of the treated groups to evaluate the Rimactazid^{R}-induced damage **(Salama *et al.*, 2018)**. They are significantly increased for drug group compared to normal and extract group's results where the results for high dose is better than that of low dose. Our results agreed with other results done by **Lian *et al.* (2013)**. The decrease in MDA and the total antioxidant levels indicates that the Moringa extract has anti-lipid peroxidation role and/or and has the ability to act against the damaging effects of Rimactazid^{R} producing free radicals. Our results are in agreement with results of **Alaaeldin (2007); Karthivashan *et al.* (2013) and Ezuruike and Prieto (2014)**. Thus it can be considered that *Moringa oleifera* leaves extract afford antioxidant properties in the oxidative stress induced by antitubercular drugs **(Bello *et al.* 2013)**.

Histopathological examination also confirmed our laboratory analysis where the group that administrated with Rimactazid^{R} show disorganization of hepatic cords and necrobiotic changes of hepatocytes characterized by focal necrotic foci and hydropic degeneration of hepatocytes. Few number micro-vesicular steatosis and apoptotic bodies were seen score IV Strongly marked increase in the number of portal lymphocytes degree 4 and this ia agreed with **Qader *et al.* (2014), Ravi *et al.* (2013) and Lian *et al.* (2013)**. In contrast the groups that administrated by Moringa extract revealed the cell necrosis of the hepatocytes in all its groups especially the MG7 and this is the same findings of **Saalu *et al.* (2012) and Sharifudin *et al.* (2013)**.

CONCLUSION

We concluded that *Moringa olifera* extract could decrease or repair the hepatotoxic effect of TB drug. From the biochemical and pathological results we noticed that the protective effect of the high dose of the extract is better than that of the low dose especially, if it used as a pretreatment method than using it used as a co-administrated or after treatment. Consequently, High dose of the Moringa extract might be used as a protective therapy with anti-tuberculosis drugs and could be even taken as a dietary supplement to protect liver from toxic effect of many chemicals because of containing a lot of antioxidant and free radicle scavenging property.

ACKNOWLEDGEMENT

It is really difficult for me to find words that can express my deep gratitude and sincere appreciation towards Asmaa Nady, Conservation Center, Grand Egyptian Museum, for his endless help, constant guidance sincere encouragement, valuable advice and criticism.

I would like to express my gratitude to Abbas goamaa due to his help.

This research did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

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