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STUDY OF THE PREVENTIVE EFFECT OF ROYAL JELLY AGAINST THE HEPATOTOXICITY OF TWO ANTI-TUBERCULOSIS DRUGS

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AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aim: Hepatotoxicity is a well-known adverse effect during treatment with antituberculosis drugs, in particular the combination of rifampicin (RMP) and isoniazid (INH).
Objective: The primary purpose of this study was to assess the contributory role of royal jelly decrease to in antituberculosis drug hepatotoxicity.
Materials and Methods: This study is an experimental study in which the preventive effect of Royal jelly on isoniazid (INH), and rifampicin (RMP) hepatotoxicity is evaluated. In this study 21 male rabbit were randomly placed in three members groups including: control group, isoniazid and rifampicin and (isoniazid (INH), and rifampicin(RMP)) /royal jelly group. At the end of the study the laboratory criteria and histological features of liver toxicity were compared in different mentioned groups.

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Results: The treatment with isoniazid/ rifampicin led to Significant increase serum levels of liver enzymes, alkaline phosphate, alat and asat; and significant higher levels of albumin total proteins and Bilirubine, in compare to mixed isoniazid/ rifampicin / royal jelly also Group and the control.
Whereas, the level of GSH concentration and enzymatic antioxidants SGSH-Px were decreased in the groups treatment by Isoniasid(INH), / rifampicin(RMP)comparative to the control grop but the MDA concentration is increased in this groups compared to addition of royal jelly are not present any significant change
In addition, histological studies had not showed liver injury in isoniazid/rifampicin/ royal jelly group, while there was liver injury in isoniazid/ rifampicin alone group.
Conclusion: The royal jelly, prevent the destructive effects of on the liver; probably because of its antioxidant properties.

Keywords: Isoniazid / rifampicin; royal jelly; livermarker; rabbit.

1. INTRODUCTION

Isoniazid (INH), and rifampicin (RMP)have been successful therapeutic agents for the treatment of tuberculosis because of their high therapeutic efficiency and good patient acceptance. However a variety of adverse reactions to these drugs have been reported: one well known toxic effect is hepatotoxicity. The risk of hepatic injury is enhanced when the two are used in combination. Steele et al reported in their meta-analysis that isoniazid and rifampicin given together produce hepatotoxicity more frequently than isoniazid without rifampicln [1].

The isoniazid metabolism mechanism which is carried out in different organs but mainly in the liver by acetylation [2]. A small part of INH is transformed directly into hydrazine, which would also be responsible for the hepatotoxicity of isoniazid [3]. This drug has toxic effects, mainly hepatic and neurological. This frequency is evaluated at 5% (Its hepatotoxicity is potentially fatal, it is increased by association with rifampicin [4], the latter which is absorbed and widely distributed throughout the body [5]. it has good diffusion tissue (bone, lung, liver, kidney, soft tissue) and good intracellular penetration [6]. rifampicin is rapidly excreted in the bile and enters the enterohepatic cycle.

Rifampicin undergoes extensive hepatic metabolism, primarily with formation of 25-o-deacetyl derivatives, is converted almost entirely to a deacetylated metabolite within approximately 6 hours. Deacetylation reduces the extent of intestinal reabsorption, which facilitates the process of elimination [5-7] it induces toxic manifestations or immunoallergic reactions. The main serious adverse events are: acute renal failure, shock and hepatotoxic hemolytic anemia, etc. [8-9].

Recently, a lot of natural plants and food supplements have been used as antioxidant agents in the different studies to prevent or treat toxicities in the various body systems that are induced by diverse toxicants. The safety, efficacy and the low price of the natural antioxidant agents in comparison with other therapeutic agents make them an excellent choice in the prevention and treatment of toxicities [10]. Like royal jelly, Royal jelly (RJ) is a honeybee product secreted from the mandibular and hypopharyngeal glands of Apis mellifera (nurse bees). This secretion is produced from sap and other plant juices and is a valuable source of antioxidants [11]. RJ is a blend of glucose, lipid, protein, minerals, vitamins [12], aspartic acid, phosphorous compounds, sterols, gel, nucleic acids, several trace ingredients, and acetylcholine, which are crucial for the nutritional and healing properties of RJ [13]. RJ has a wide range of pharmacological applications including use as an immune-stimulant [14], a potent antioxidant [12], and a hepatoprotective agent [15]. Furthermore, RJ has antitumor, hypoglycemic, antibacterial, antihyperlipidemic, and anti-inflammatory properties [16].

2. MATERIALS AND METHODS

2.1 The Royale Jelly

The royale jelly were collected from North-East of Algeria (khenchela) during spring

2.2 Experiment Design

Male rabbet (1860±220 g) was purchased from Pasteur Institute, Algiers. Animals were maintained under standard conditions of temperature and humidity with 12 h light/dark cycle and fed standard pellet diet and water *ad-libitum* for two weeks as an adaptation period. Then rabbet were randomly divided into three groups of seven animals each

- Group (C): control group received only physiological water by force-feeding
- Group (R/H): each rabbit received a volume of 2ml of isoniazid/rifampicin of Concentration (75/150 mg) orally (gavage) for 15 successive days

- Group (R/H+RJ): rabbits treated with 2ml isoniazid/rifampicin (75/150 mg) and 2ml royal jelly (10mg/ml)/ 15 successive days

At the end of the experimental period, animals were sacrificed by decapitation after overnight fasting. Plasma was separated by centrifugation for 10 minutes at 3000 rpm and stored at -20°C for the biochemical analysis. The livers were removed immediately, rinsed with ice cold saline 0.9%. Then, one part was homogenized in 2 ml ice cold Tris Buffered Saline TBS (50 mM Tris, 150 mM NaCl, pH 7.4). The homogenates were centrifuged at 10.000 g for 15 min at 4°C and the resultant supernatant was frozen at -20°C for oxidative parameters determination. The other part was fixed in 10% neutral formalin and used for the histological examination.

2.3 Analytical Methods

2.3.1 Determination of biochemical parameters

Transaminases (Glutamic Pyruvic Transaminase: GPT, Glutamic Oxaloacetic Transaminase: GOT), Alkaline Phosphatase (ALP) total proteins, total bilirubin, were assessed using Spinreact Laboratory Spain diagnostic kits and spectrophotometer (Jenway 6505, Jenway LTD, Essex, UK).

2.3.2 Reduced glutathione (GSH) concentration

Liver GSH content was estimated using a colorimetric technique, as mentioned by Jollow et al. [17] based on the development of yellow color when 5,5- Dithiobis-(2-Nitrobenzoic Acid) (DTNB) is added to compounds containing sulfhydryl groups. The absorbance was recorded at 412 nm. Total GSH content was expressed as nmol GSH/mg protein.

2.3.3Antioxidant enzymes assays

Glutathione peroxidase activity (GSH-Px) was assayed by the method based on the reaction between glutathione remaining after the action of GSH-Px and 5, 5-Dithio-bis (2-nitrobenzoic acid) DTNB to form a complex that absorbs maximally at 412 nm.

2.2.4 Hepatic proteins content

Protein was measured by the method of Bradford [18], using bovine serum albumin as a standard.

2.4 Liver Histopathology Examination

Histological evaluation was performed on a lobe of the liver and portion of specimen fixed in 10% formalin and embedded in paraffin wax. Then sections were cut at 4 μm in thickness, stained with hematoxylin and eosin and viewed under light microscope for histological changes [19].

2.5 Statistical Analysis

Data are given as means ± SEM. Statistical significance of the results obtained for various comparisons was estimated by Student's t-test and the level of significance was set at $p<0.05$.

3. RESULTS

3.1 Effect on Biochemical Parameters

According to the results obtained (tab. 01, we observe a significant increase in the serum concentration of total protein and a highly significant increase in the concentration of albumin and bilirubin in the group treated with (isoniazid (H), and rifampicin (R)) comparing to the control group, on the other hand, no significant change is recorded concerning these parameters in the batch treated with (R/H) and royal jelly (RJ) compared to the control.

3.2 Estimation of Liver Marker Enzymes in Liver

We note a significant increase in the levels of GOT and GPT enzyme and highly significant in the levels of alkaline phosphatase enzyme in the batch treated with (R/H) compared to the control, on the other hand that in the batches treated with royal jelly and (R/H) the level of GOT and ALP enzymes does not show any significant change, while the concentration of GPT shows a significant increase compared to the control batch.

3.3 Effects of Treatments on Hepatic Oxidative Stress Parameters

3.3.1 Malondialdehyde (MDA) levels

According to the results illustrated in figure 01-A, a significant increase ($p\leq0.05$) in the level of hepatic MDA is observed in the group treated with INH/RMP compared to the control rabbits, while the supplementation of the royal jelly or INH/RMP leads to a non-significant decrease in hepatic MDA levels. We note that the concentration of MDA in the organ studied returns almost to the normal state and there is no significant variation in this activity in the batch treated with royal jelly and INH/RMP in comparison with the group witness.

Table 1. Changes of biochemical parameters of control male rabet, treated with (isoniazid (INH), and rifampicin(RMP); isoniazid (R/H)and royal jelly, after 2 weeks of treatment

	C	R/H	R/H+RJ
Total protein(g/dl)	65,4±6,77	72,43±5,86*	65,33±5,91
Albumine (g/dl)	25 ,33±2,64	32,1±0,66**	27,38±1,77
Bilirubine (mg/dl)	0.66±0.06	1.25±0.12**	0.87±0.09
GOT (U/L)	38,25±4,11	52,75±3,24*	37,50±4,51
GPT(U/L)	35,50±2 ,52	67,30±3,92*	41 ,25±3,67*
ALP(U/L)	770±46,3	872,8 ±41.95**	755±75,4

3.3.2 Reduced glutathione (GSH) levels

Treatment of rabbits with INH/RMP, at one dose, leads to a highly significant decrease ($p \leq 0.01$) in hepatic glutathione content. On the other hand, in the groups treated with the INH/RMP combinations and royal jelly, there is no significant difference in the level of GSH at the level of the organ studied compared to the control group (Fig. 1-B).

3.4 Glutathione Peroxidase (GSH-Px) Activity

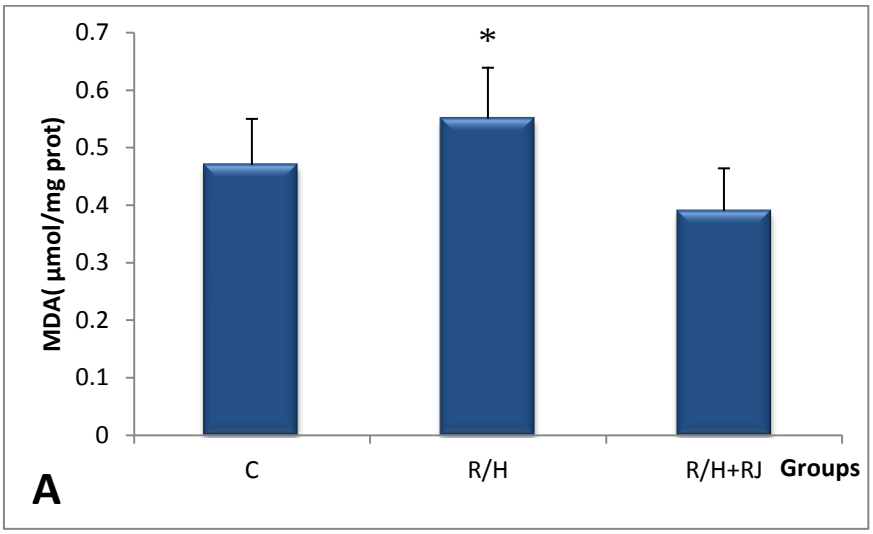
According to figure 01-c, it can be seen that the treatment of rabbits with INH/RMP causes a significant decrease ($p \leq 0.05$) in the activity of GSH-Px in the hepatic tissue, compared to control rabbits Moreover, the batches treated only with INH/RMP and royal jelly the level of GSH-Px did not lead to any significant change in the liver compared to the control.

3.5 Hepatic Histoarchitecture

Microscopic observation of group C liver reveals normal tissue architecture; the centrally located centrilobular vein is surrounded by normal hepatocytes, the latter are organized into hepatocyte trabeculae crossed by sinusoidal capillaries (Figure 2.TX 100). At high magnification, we note the presence of clear polyhedral hepatocytes (Figure 2.TX 400).

Microscopic observation of group L1 liver tissue treated with INH/RMP showsvery important tissue alterations in comparison with the T group, degenerationhepatocyte cell and necrosis at low magnification (Figure 2.RHX 100.).

Strongmagnification, there is a dilation of the centrilobular vein, tissue necrosis, a hemorrhage in the light of the centri-lobular vein and central vein is also at Sinusoid level (Figure 2 RH X 400) The histological section performed on the liver of the INH/RMP and GR treated group reveals less significant tissue damage compared to the INH/RMP group. At low magnification, the tissue architecture appears normal and only reveals a dilation at the level of the central vein (Figure 2. RH/RJ X 100.). However, at high magnification, some cellular degeneration of hepatocytes is recorded in a few places (Fig. 2. RH/RJ X 400).



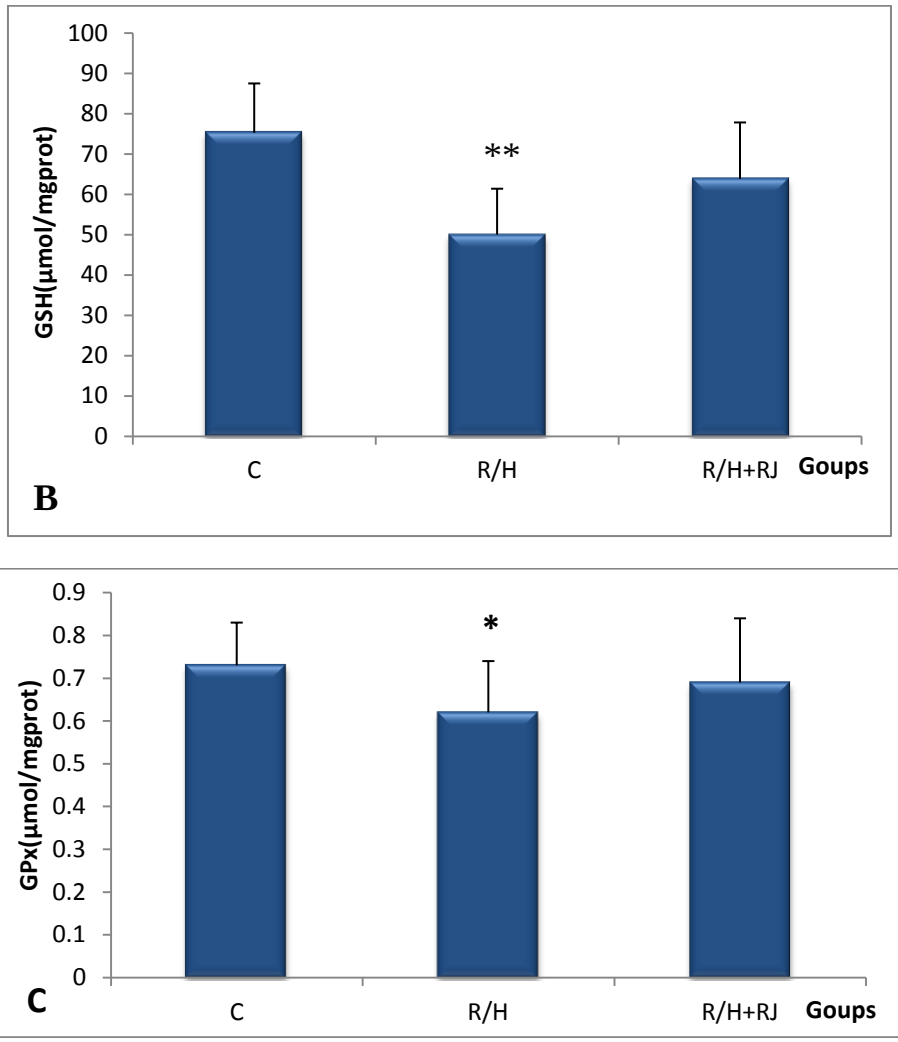
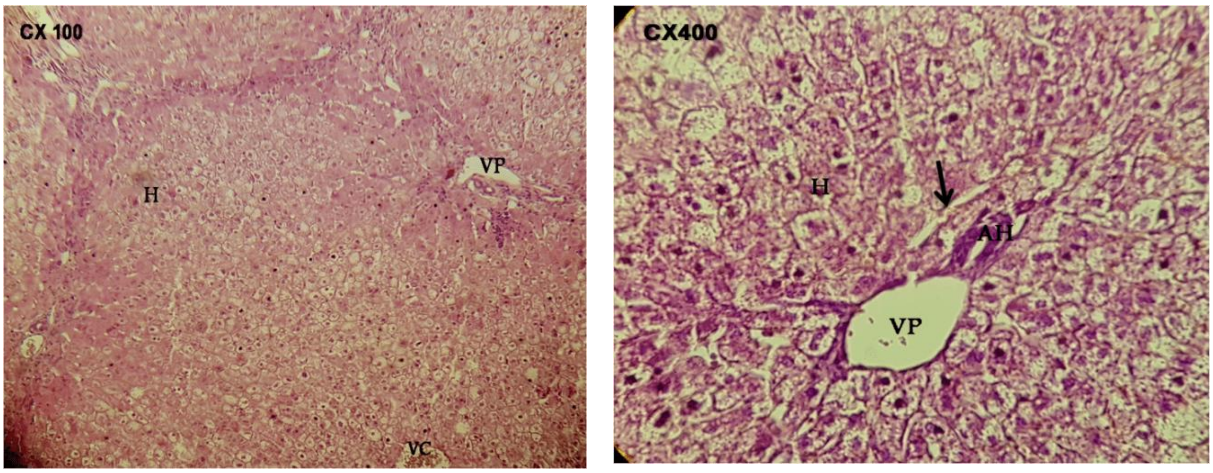


Fig. 1. Values of malondialdehyde glutathione, and GSH-Px in liver of control and rabbet treated with isoniazid (INH), and rifampicin(RMP) ; isoniazid (INH/RMP) and royal jelly, after 15 days of treatment



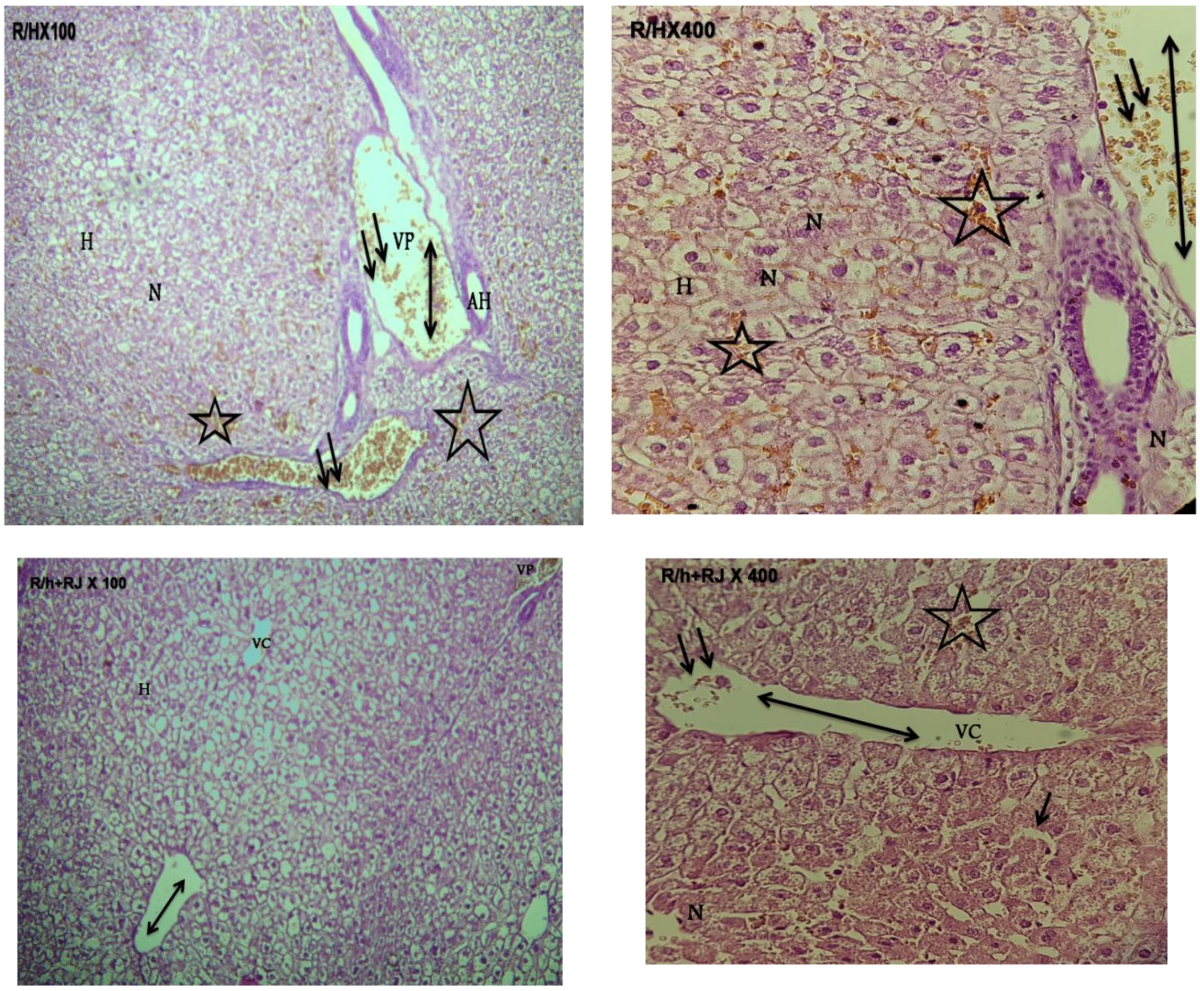


Fig. 2. Microscopic observation of histological sections of the liver in control rabbits (c) and rabbits treated with rephampicin/isoniasid (R/H) and combinations R/H and royal jelly (R/H+RJ) after 15 days of treatment (Gr x 100 and x400). Hematein-eosin staining

Sinusoid ↘ Sinusoid haemorrhage ☆ Hemorrhage ⇊ dilation ⇕

H. Hepatocyte N. Necrosis VC. central vein. VP. portal vein

4. DISCUSSION

Anti-tuberculosis drugs are responsible for frequent and potentially serious adverse effects, which necessitate precautions during initiation and monitoring during continuation of treatment [20-21]. In this context, this study aims to highlight, on the one hand, the hepatotoxic effects of the two anti-tuberculosis drugs: isoniazid (INH) and rifampicin (RMP) on certain liver functions, and on the other hand to verify royal jelly. Showing beneficial effectsthe results of our study show that the treatment of rabbits with antituberculosis drugs for two weeks induces an alteration of the biochemical balance (total protein, albumin and bilirubin), transaminases (ASAT, ALAT) and alkaline phosphatase (ALP) which are biomarkers liver function [22], increased serum bilirubin levels in milked rabbits is a clear marker of liver dysfunction, or A disorder of bilirubin metabolism is caused either by an enzyme deficiency, or by a physical obstruction flow of bilirubin such as biliary obstruction (bile duct). Hyperbilirubinemia leads to kernicterus [23] These results are in agreement with the results of Aouam [24].

The results revealed a highly significant increase in serum total protein and albumin concentration in the R+H treated group compared to the control group due to the inhibitory effect of isoniazid on the potent cytochrome P450. This results in a decrease in the hepatic catabolism of possibly associated drugs (vitamin K antagonist, phenytoin, carbamazepine, stavudine, ketoconazole) and an increase in their plasma concentrations occurs with a risk of toxicity. If isoniazid does not modify the metabolism of rifampicin, the latter induces that of isoniazid with a risk of accumulation of hepatotoxic metabolites explaining the potentiation of the hepatotoxicity of isoniazid by rifampicin [25-26], On the other hand there are similar studies in rats treated with isoniazid (50 mg / kg) show that the treatment of isoniazid to lead to disturbances of the hepatic parameters which is manifested by a decrease in the level of albumin and total protein [27]. Other studies showed that serum albumin and total protein levels decreased in rats treated with (INH: 90mg/kg and RMP: 250mg/kg) for 15 days [28].

In the present study, we found an increase in ALT in rabbits treated with INH/RMP compared to control rabbits; this is related to the hepatotoxic effect of INH/RMP. This increase causes liver cells to be damaged, which dump their contents such as transaminases into the blood [29].

These antituberculosis drugs are metabolized to reactive metabolites also leading to necrosis [30]. Severe, hepatic cell cytolysis, and inflammatory infiltration [27]. We also found a recovery of plasma ALT levels after administration of royal jelly to rabbits treated with INH/RMP. This interpretation is reinforced by results obtained by Hajimehdipoor et al. [31];who demonstrated that royal jelly inhibited the hepatotoxic effects induced by cisplatin. Similarly Karadeniz et al (2011) reported the same results in rats treated with paracetamol. Overall [32].

The results obtained in the present work indicate that royal jelly protected the liver tissue against the toxic effects of INH / RMP because of their richness in vitamins such as vit A and E which are antioxidant activity and otherwise, the composition flavonoids (catechin and epicatechin) from the jelly and dipeptides (Phe-Asp, Trp-Leu) have a protective effect, i.e. instead the free radicals produced by antituberculosis drugs are neutralized by Glutathione they will rather be captured by the royal jelly, thus maintaining the normal level of hepatic glutathione [33-34]. What explains our results concern the variation in antioxidant levels at the liver tissue levels. Microscopic observation of liver tissue revealed inflammatory cell infiltration around the portal vein and artery with clear cytoplasm and hepatocyte degeneration. haemorrhage, liver damage in the tissue sections of the liver of rabbits treated with INH/RMP therefore the liver is the organ for the metabolism of various toxic components These results are similar to those of Hossein et al. [35]. The administration of royal jelly reduced liver damage and the number of inflammatory cells. Similar studies carried out in Albino Wistar rats, received a combined treatment with (cisplatin +300mg/kg/day of royal jelly) for 14 days show that royal jelly attenuated certain harmful effects of Formaldehyde (hepatic necrosis, inflammation) [36] and also Rasha et al. [37] confirmed the beneficial effects of royal jelly on diclofenac hepatortoxcict in rats.

5. CONCLUSIONS

According to our results, we were able to confirm that royal jelly has a very important role against antituberculous drugs given these antioxidant properties against hepatotoxicity.

DISCLAIMER

The productsused for thisresearch are commonly and predominantly use products in our area of research and country. There isabsolutely no conflict of interestbetween the authors and producers of the productsbecausewe do not intend to use theseproducts as an avenue for anylitigation but for the advancement of knowledge. Also, the researchwas not funded by the producingcompanyratheritwasfunded by personal efforts of the authors.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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