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ORIGINAL ARTICLE

PROPOLIS-INDUCED HEPATORENOPROTECTION IN RODENTS EXPOSED TO RIFAMPICIN AND ISONIAZID

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Summary

The elimination of most drugs based on liver/renal excretion; making liver and kidneys the commonest target organ for exposure to toxic materials. Long-term use of drugs surpassed the effect and aggravate the toxicity. Tuberculosis (TB) is chronic disease with long-term therapy and the deleterious impact of antitubelculosis is certain. Various pharmacokinetic manoveuors were proposed to avoid the potential harmful effect of TB therapy. The present study aimed at mitigating the destructive effects of TB therapy using propolis. To do so, rats were exposed to isoniazid or rifampicin or a combination of them in groups of 8 rats each for a period of 8-weeks these groups were matched with similar group with a propolis ad-on therapy. These results were compared to propolis-free negative control group and positive propolis-treated group. The histological and laboratory findings confirmed that isoniazid or rifampicin or a combination of them jeopardized hepatorenal function and induced deleterious damage. However, isoniazid has shown more intensive deleterious effect compared to rifampicin. Nonetheless, propolis restore the quasi-equilibrium status for kidney and liver via restoring its normal architecture and functionality. To sum up, the potential defect of anti-TB was restored via using propolis as add-on therapy, we do advise using propolis as an adjuvant TB therapy in critically–ill and clinical cases required long-term TB therapy.

Key words: isoniazid; rifampicin; propolis; liver; kidney

Introduction

One of the most common causes of death, in today's era, is liver diseases and renal diseases (1). Detoxification of xenobiotics metabolism is done by the liver and it is also responsible for the clearance functions of drugs. As well as the harmful chemical compounds from the blood are being cleared with its help. Xenobiotics and chemical molecules and its free radicals are responsible for oxidation stress. It may cause the liver function abnormalities which ultimately lead towards to liver damage (2). Drug induced hepatotoxicity is being caused as the result of large number of drugs and chemical compounds in which some prescribed medications are also involved, is one

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of the concerning problems in today's time (3). Most widely used anti-tuberculous medication linked with acute interstitial nephritis is rifampin but it is not so common (4). Many adverse effects are also associated with the drug rifampin. Those adverse effects usually appear in patients who have previously taken the drug or received intermittent treatment (5, 6).

Some common drugs that are being used in chemoprophylaxis and management of TB include Rifampicin (R), isoniazid (IHN), pyrazinamide, and ethambutol (7). Some of the most important first line drugs for treatment of tuberculosis include Rifampicin, isoniazid, streptomycin, ethambutol, pyrazinamide. Liver toxicity is also found to be reduced using these important first line drugs (7). Furthermore, for the study of hepato-toxicity, rifampicin/isoniazid induced toxicity is the one most commonly used framework. The antitubercular therapy in most of the patients is bearable but also side effects in some of the patients could be seen. These side effects ultimately lead towards hepatotoxicity (8, 9). Due to this antitubercular therapy, about 9.5 % patients develop hepatotoxicity in India, according to the studies being done till now (10). Hence, it is important to find a substitute, safe, powerful and economical drug to fight the poor impacts of the present modern antitubercular therapy drugs that are commercially available.

Different products could be made by using Honey Bee that can be collected from different plants species. Bee Propolis is one of them. It is a balsamic resin. Egyptians, Romans and Persians have been using propolis as a medicine for the treatment of various diseases over many years (11). More than 500 bioactive molecules have been identified and isolated from propolis according to the studies. Flavonoids, phenolics, volatile oil, terpenes, aromatic compounds and bee wax presence have been proven by phytochemical investigation means (12). Antimicrobial activity, antidiabetic activity, anticancer potential, anti-inflammatory property, antioxidant property, antihypertensive effect, and immunostimulant activity are the biological activities that have been outlined on propolis (13-17).

Materials and Methods

The study has been carried out using 64 Sprague Drawly rats (male; mature at age 10-12 weeks; average weight 250 g). They were maintained under standard laboratory condition of water-food-light which is adopted by animal house in the College of Veterinary Medicine in the University of Mosul. They were divided into 8-groups of 8-members each. Each group were treated by the specified agent(s) and given the name accordingly (Table 1).

Table 1. Studied group identification.

	Group Name (n=8, each)							
	C	P	INH	INH+P	R	R+P	INH+R	INH+R+P
Normal Saline	*							
Isoniazid			*	*			*	*
Rifampicin					*	*	*	*
Propolis		*		*		*		*

The drugs used in the present studies were purchased locally from well-known pharmaceutical company. The dose used and origin of used medication outlined in Table 2.

Table 2. Dose, origin and supplier's details of used medication in the present study.

Medications	Trade Name	Suppliers	Origin	Dose
Isoniazid	INH	KOCAK pharmaceuticals	Turkey	50mg/Kg/day
Rifampicin	Sinerdol	Antibiotice pharmaceuticals	Romania	100mg/Kg/day
Propolis	Propolis	NOW FOODS pharmaceutical	USA	200mg/Kg/day

Serum sample collected from individual animal initially (baseline). The second serum sample collected after 8 weeks of continuous drug administration (see Table 1 and dose in table 2). Collected serum samples were analyzed

biochemically and animal sacrificed for histopathological study. Kidney and liver collected from sacrificed animal in clean container supplied with 10% formalin for fixation.

Biochemical analysis was conducted on serum samples through measurement of liver function test and renal function tests. The measured parameters outlined in Table 3 with specified kits identity and suppliers with country of origin.

Table 3. Kits and suppliers used in the present study.

Medications	Catalogue No.	Suppliers	Origin
ALT	AT-92025	Biolabo	France
AST	AT-92027	Biolabo	France
ALP	AT-80014	Biolabo	France
Albumin	AT-80002	Biolabo	France
TSB	AT-80403	Biolabo	France
Creatinine	AT-80107	Biolabo	France
Urea	M11536c-16	BioSystems	Spain
Uric acid	AT-80001	Biolabo	France

Results

The assessment of propolis positive hepatorenoprotection effects in rat model, serum samples collected and analyzed before and after exposure to isoniazid and/or rifampicin followed by sacrificing the animal for histopathological assessment of the kidneys.

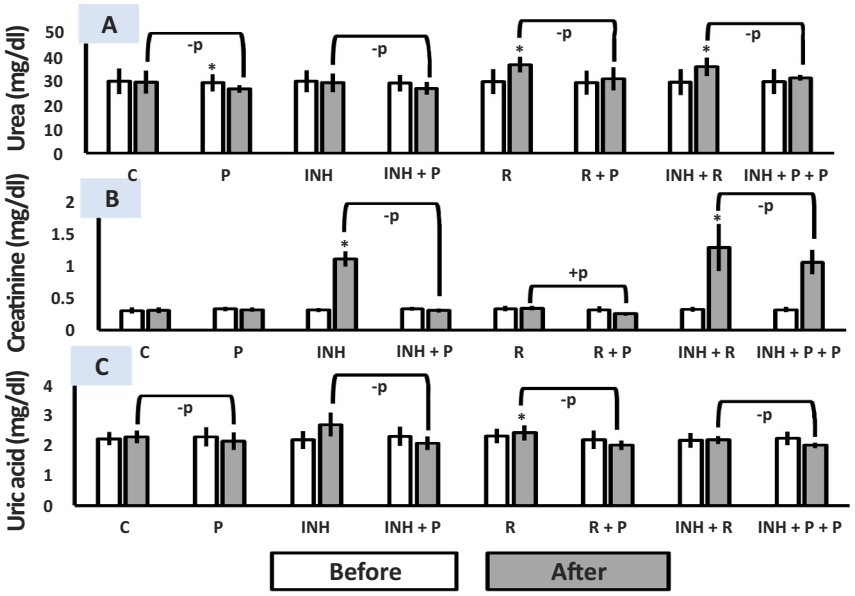

Figure 1. Propolis blocked renal damage induced by rifampicin and/or isoniazid in experimental rat model. Serum was collected from rats exposed to rifampicin and/or isoniazid in propolis-free or propolis-treated groups and renal function test assessed. Renal parameters quantified based on determination of the serum level of urea, creatinine, and uric acid. Data expressed as mean ± SD. $^{-p}$<0.05 significantly higher in propolis-free group as compared to propolis-treated group. *p<0.05 as compared to before/after therapy of the same group and condition. C=control, p= propolis, INH=isoniazid, R=rifampicin.

Regarding blood urea levels; there were non-significant (p<0.05) differences between all groups before initiation of the therapy whether in propolis-treated or propolis-free therapy; the levels in all groups were close to the negative

control group (Figure 1A). Positive control propolis-treated group shown significantly lower blood urea level compared to control negative propolis-free group or to the propolis-treated group before starting propolis therapy. In the other hand, blood urea levels were significantly elevated in propolis-free experimental animals following their exposure to either rifampicin or a combination of rifampicin and isoniazid, nonetheless, the effect was negligible when isoniazid used alone. However, blood urea levels were significantly reduced in propolis-treated experimental animals following their exposure to either rifampicin or a combination of rifampicin and isoniazid (Figure 1A). Similarly, propolis has significantly reduced creatinine in groups exposed to rifampicin and/or isoniazid ($p<0.05$) when compared to propolis-free therapy (Figure 1B). Propolis has significantly reduced uric acid in groups exposed to rifampicin and/or isoniazid ($p<0.05$) when compared to propolis-free therapy (Figure 1C) with non-significant differences exists between propolis treated group compared to levels in negative control group.

Propolis has significantly ($p<0.05$) reduced the increase in the dilation in proximal/distal convoluted tubules produced by isoniazid or rifampicin or a combination of them. Isoniazid and rifampicin has significantly ($p<0.05$) reduced the diameters of glomeruli compared to negative control. Rifampicin and isoniazid or a combination of them has significantly increased the Bowmans space whereas propolis treated groups shown significant ($p<0.05$) lower values regarding these histological parameters (Figure 2).

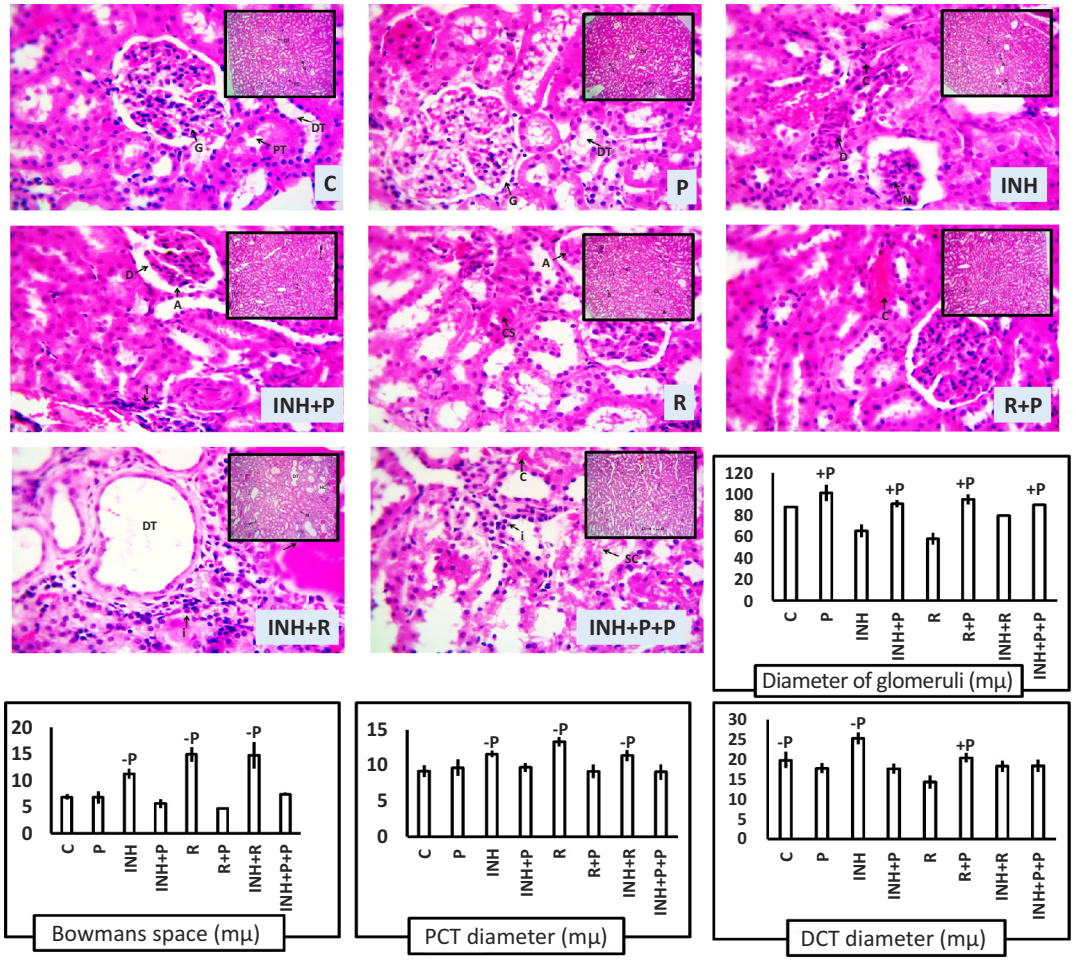

Figure 2. Propolis blocked histological damage induced by rifampicin and/or isoniazid in experimental rat model. Rats exposed to rifampicin and/or isoniazid in propolis-free (Small images) or propolis-treated (Large images) groups were sacrificed and their kidneys were fixed for histological studies. Renal parameters quantified based on determination of the size of proximal and distal convoluted tubules together with the size of glomeruli and Bowman capsule. Data expressed as mean ± SD. $^{+p}<0.05$ significantly higher in propolis group as compared propolis-free group. $^{-p}<0.05$ significantly higher in propolis-free group as compared to propolis-treated group. C=control, p=propolis, INH=isoniazid, R=rifampicin.

The microscopic evaluation of kidneys revealed structural changes induced by rifampicin and isoniazid which then start to reduce with propolis therapy. Both INH and rifampicin induced moderate glomerular atrophy which has been mitigated to mild stage in the same treated agents after addition of propolis therapy. INH moderately dilate Bowman's space which are reduced to mild stage with propolis therapy.When INH and rifampicin combined they do moderately induced Vacuolar degeneration and cell swelling, induced Hyaline casts, and tissue necrosis, nonetheless, their combination with propolis has reduced the isult into mild degree (Table 4).

Table 4. Microscopic-based evaluation of histopathological kidney sections in the studied groups.

No.	Kidney pathological parameters	C	P	INH	INH+P	R	R+P	INH+R	INH+R+P
1	Atrophy of glomeruli	-	-	++	+	++	-	+	+
2	Segmentation of glomeruli	-	-	-	-	-	-	-	-
3	Dilation of Bowman's space	-	-	++	+	+	-	+	+
4	Vacuolar degeneration and cell swelling	-	-	+	-	+	-	++	+
5	Hyaline casts	-	-	-	-	-	-	++	-
6	Pyknosis of nucleus	-	-	-	-	-	-	+	-
7	Necrosis	-	-	-	-	+	-	++	-
8	Apoptosis	-	-	-	-	-	-	-	-
9	Inflammation (infiltration of inflammatory cell)	-	-	+	+	+	-	+	+
10	Hemorrhage	-	-	-	-	-	-	-	-
11	Congestions	-	-	+	-	+	+	+	+
12	Cystic kidney formation	-	-	+	-	-	-	+	-
13	Fibrosis	-	-	-	-	-	-	-	-

Sever (+++); Moderate (++); Mild (+) and No change (-ve)
C=Control; P=Propolis; INH=isoniazide; R=rifampicin

Regarding blood ALT levels; there were non-significant ($p<0.05$) differences between all groups before initiation of the therapy whether in propolis-treated or propolis-free therapy; the levels in all groups were close to the negative control group (Figure 3A). Positive control propolis-treated group shown significantly lower blood ALT level compared to control negative propolis-free group or to the propolis-treated group before starting propolis therapy. In the other hand, blood ALT levels were significantly elevated in propolis-free experimental animals following their exposure to either rifampicin or a combination of rifampicin and isoniazid, nonetheless, the effect was negligible when isoniazid used alone. However, blood ALT levels were significantly reduced in propolis-treated experimental animals following their exposure to either rifampicin or a combination of rifampicin and isoniazid (Figure 3A). Similarly, propolis has significantly reduced AST in groups exposed to rifampicin and/or isoniazid ($p<0.05$) when compared to propolis-free therapy (Figure 3B). Propolis has significantly reduced ALP in groups exposed to rifampicin and/or isoniazid ($p<0.05$) when compared to propolis-free therapy (Figure 3C) with non-significant differences exists between propolis treated group compared to levels in negative control group. Propolis has significantly reduced TSB in groups exposed to rifampicin and/or isoniazid ($p<0.05$) when compared to propolis-free therapy (Figure 3D) with non-significant differences exists between propolis treated group compared to levels in negative control group. Surprisingly, propolis reduced albumin weather in presence or absence of either isoniazid or rifampicin or both (Figure 3E).

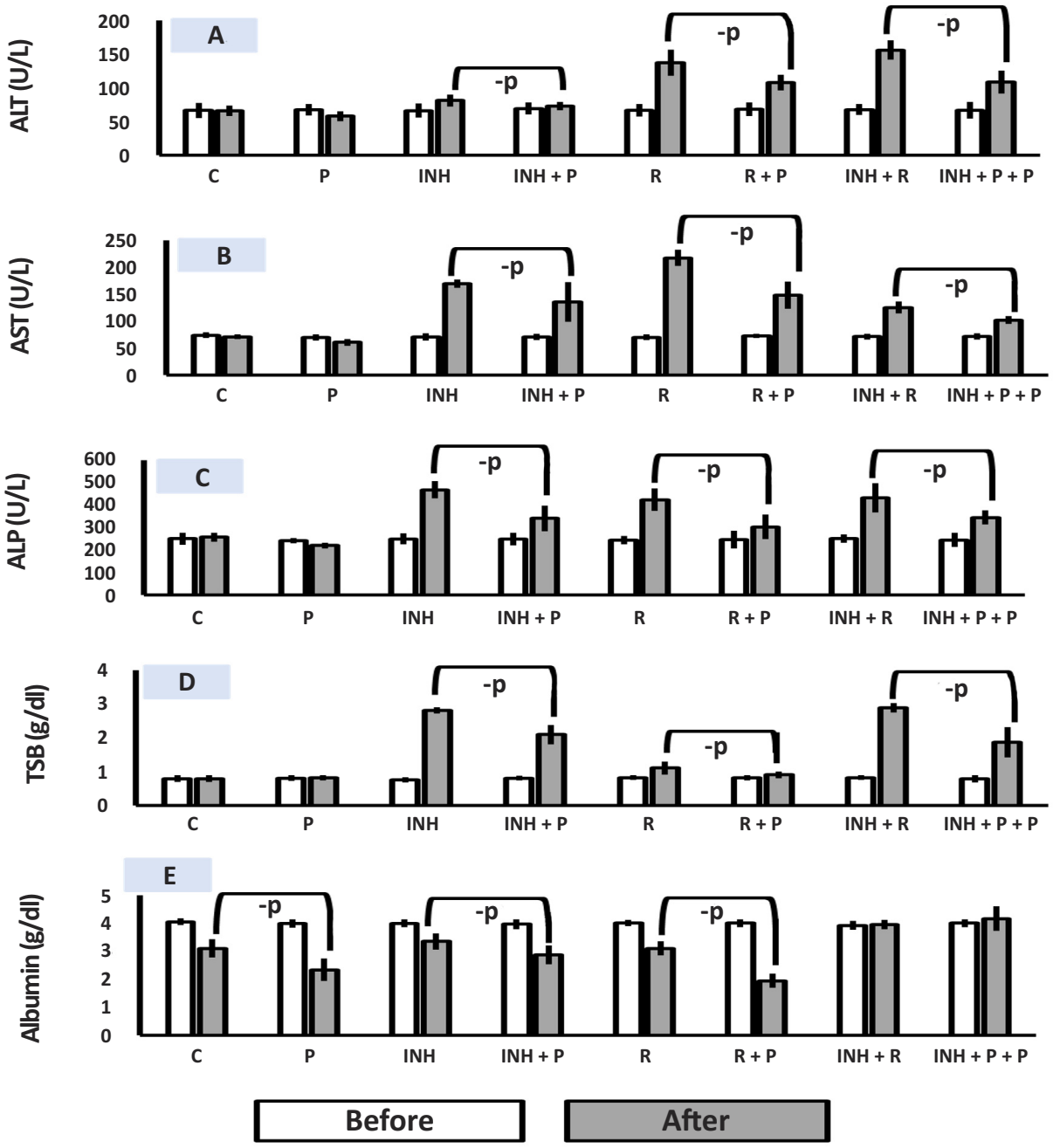

Figure 3. Propolis blocked liver damage induced by rifampicin and/or isoniazid in experimental rat model. Serum was collected from rats exposed to rifampicin and/or isoniazid in propolis-free or propolis-treated groups and renal function test assessed. Renal parameters quantified based on determination of the serum level of ALT, AST, ALP, TSB, and albumin. Data expressed as mean ± SD. -p<0.05 significantly higher in propolis-free group as compared to propolis-treated group.*p<0.05 as compared to before/after therapy of the same group and condition. C=control, p= propolis, INH=isoniazid, R=rifampicin, AST=Aspartate transaminase, ALT=alanine transaminase, ALP=Alkaline phosphatase, and TSB=Total serum bilirubin.

Weight measured in all treated group. Despite of low variation between groups, however, rifampicin and INH has induced slight changes in the weight of liver, kidneys, and body weight. These effects have blocked by propolis (Figure 4).

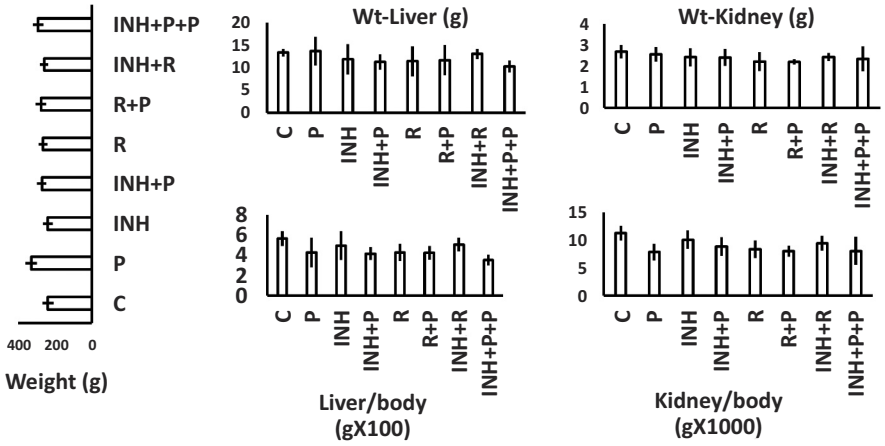

Figure 4. Weight changes associated with exposure to INH/rifampicin. Rat weight, liver weight, kidney weight, liver to body ratio, kidney to body ratio. C=control, p= propolis, INH=isoniazid, R=rifampicin.

Liver histopathology has been carefully studied and the outcome has shown significantly dilated sinusoids in presence of either rifampicin or isoniazid or a combination of both. Propolis has reduced sinusoid dilation into normal size. The number of Kupffer cells significantly higher in presence of propolis versus propolis-free group indicating positive immunomodulation achieved by propolis therapy (Figure 5 and Table 4).

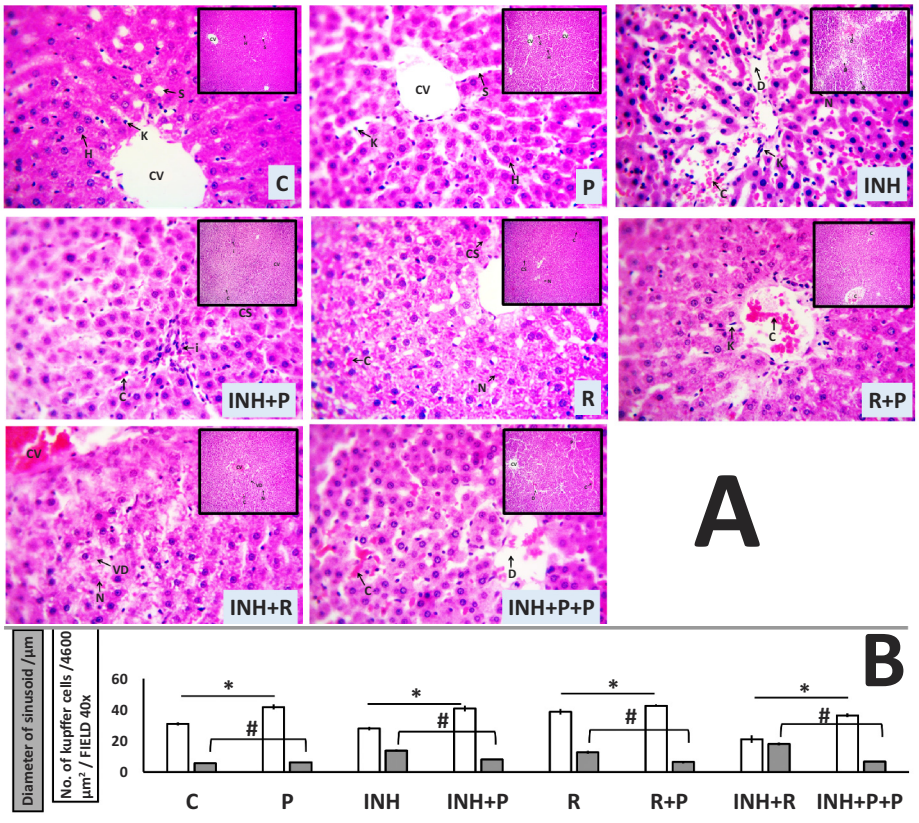

Figure 5. Propolis reduced histological damage providing protection against exposed drugs. While bars=Number of kupffer cells /46000 µm²/FIELD, Grey bars=Diameter of sinusoids /µm. A) histological section of treated groups B)histopathological parameters quantifyinhg the damage. C=control, p=propolis, INH=isoniazid, R=rifampicin. Data expressed as mean ± SD. *<0.05 significantly higher in propolis group as compared propolis-free group. #<0.05 significantly higher in propolis-free group as compared to propolis-treated group.

Table 5. Microscopic-based evaluation of histopathological kidney sections in the studied groups.

No.	Liver pathological parameters	C	P	INH	INH+P	R	R+P	INH+R	INH+R+P
1	Hepatic portal pattern	-	-	-	-	+	-	+	-
2	Hepatic sinusoids dilation	+	-	++	-	-	+	+	+
3	Fatty changes	-	-	-	-	-	-	-	-
4	Vacuolar degeneration and cell swelling	-	-	+	+	+	-	++	-
5	Pyknosis of nucleus	-	-	+	-	+	-	+	-
6	Necrosis	-	-	+	-	+	-	++	-
7	Apoptosis	-	-	-	-	-	-	-	-
8	Inflammation (infiltration of inflammatory cell)	-	-	+	+	+	-	+	-
9	Hemorrhage	-	-	+	-	-	-	-	-
10	Congestions	-	-	++	+	+	+	++	+
11	Hyperplasia of bile ducts	-	-	-	-	-	-	-	-
12	Hypertrophy of hepatocytes	-	-	-	-	-	-	-	-
13	Fibrosis	-	-	-	-	-	-	-	-

Sever (+++); Moderate (++); Mild (+) and No change (-ve)
C=Control; P=Propolis; INH=isoniazide; R=rifampicin

Discussion

The biochemical findings of renal and liver function tests together with histological study revealed that propolis has provided a protection against modulation induced by isoniazid and rifampicin though measured parameters. Drug side effects on various vital organs has been reported, antipsychotics affect immunity (18), allopurinol on metabolic parameters (19) and thyroid function (20), statins on platelets (21) and metabolic parameters (22), antidiabetics on thyroids (23), non-steroidal anti-inflammatory drugs on gastric mucosa (24), proton-pump inhibitors on kidneys (25) and metabolic parameters (26). These effects depicted in our locality and using propolis as an add-on therapy might restore the defective actions.

Our present study has demonstrated the deleterious impact of both rifampicin and isoniazid on the liver and kidney in term of functionality and structural architecture which has been confirmed by histological and laboratory measurements, these deteriorating effects has been documented earlier though in vitro studies conducted on rodents; rifampicin and isoniazid-induced toxicity which is supposed to alter the liver cellular defense mechanisms, by both enzymatic and non-enzymatic means has been outlined (27). N-acetyl transferase, acetylhydrazine, and isonicotinic acid are found to be produced during the acetylation of isoniazid by the liver enzyme. Moreover, hydrazine and diacetylhydrazine is produced by acetylhydrazine on hydrolysis. Both the metabolites are roots of irretrievable cellular injury (28, 29). Desacetyl-rifampicin is being metabolized by rifampicin in liver. Desacetyl-rifampicin then on further hydrolysis is formed into 3-formyl rifampicin which is accountable for hepatocellular injury (30). Increased levels of enzymes (SGOT, SGPT, ALP, and total bilirubin) from the liver and reduction in total protein in blood are the results of hepatocellular injury (31). Reduction in scavenging capacities and capabilities of the hepatocytes causes the increase in concentration of free radicals in the body (32). Increase in free radicals and decline of scavenging capacity of hepatocytes leads towards increased level of oxidative stress (33). Reactive

oxygen metabolites and lipid peroxidation possibly could be the potential cause for several hepatic cellular injuries revealed by histological changes in liver in many studies. Lipid membranes of liver are covalently bounded by acetylated product of INH, acetylhydrazine, and could be the reason of oxidative deterioration of lipids. It ultimately leads towards adipose tissue displacement in the hepatic cells (34). The recovery of hepatocytes from steatosis, necrosis and inflammation in comparison to toxic group and in comparison to normal group is showed by the photomicrographical examination. Furthermore, against invasive microorganisms and chemicals to regulate body healthiness, inflammation is a self-protective reaction, therefore, tissue degradation is caused by the inflammatory progression that ultimately goes towards the path of many disorders (27).

In one study, 41 patients had a long-standing diagnosis of acute interstitial nephritis, in a retrospective study done between the years 1995 and 2007. An intermittent regimen of anti-tuberculous therapy having rifampin was given to the patients. Rifampicin's capability to generate an immune response is related to the link of exposure of the therapy, which then causes cell destruction (35). By generating anti-rifampicin antibodies, rifampicin functions as a substance that is bounded to the proteins, causing immune response (4). As the consequences, the patient's body generates drug antibody complexes in response to the subsequent exposure of rifampicin, leading towards cell destruction. Tubular injury and a reduction in renal function is caused by the result of cellular destruction and glomerular endotheliosis which is led by the immune complexes, found in a study in which 25 patients were involved (36). A clinical diagnosis related to rifampin usually suggests acute renal injury. When renal failure forms in the setting of exposure to an offending agent, biopsy is usually not necessary for diagnosis investigated by Beck and Salant (37). One of the most usual findings is acute interstitial nephritis or acute tubular necrosis when biopsy is carried out (34, 38). Patients with biopsy-proven acute interstitial nephritis who were on chemotherapy for tuberculosis from South Africa Schubert's series were involved only. Acute interstitial infiltrate was found to be available in all cases of 41 patients in a study as well as acute tubular necrosis was also observed in 90 % patients. Various kidney diseases were also found to be linked with the drug rifampin, one of which includes diffuse proliferative crescentic glomerulonephritis (36). Acute renal failure related with rifampin is also caused by immune-mediated acute interstitial nephritis. Despite the fact that the diagnosis of acute interstitial nephritis is good having 1.6 % mortality rate, it still remains a complex issue that could lead to Fanconi syndrome, a proximal renal tubule defect leading to malabsorption of phosphorus, bicarbonate, sodium, potassium, glucose, and amino acids. It eventually results in different symptoms that involve bone pain and fracture, fatigue, and muscular weakness. Acute interstitial nephritis caused by Rifampin was not proven in spite of the etiology of the patient's acute renal failure. Acute kidney injury was particularly by chance that could be a common introduction (37). The patient did not have to be found with the common symptoms of fever, nausea, vomiting or elevated liver enzymes on some series note (34, 36). Surprisingly, mild hepatitis and nausea was in the start developed, but these symptoms intent onto finding the elevated creatinine. Eosinophilia and eosinophils were not found in the urine of the patient. In urine, no white or red blood cells were found. No renal biopsy was performed. Corticosteroid therapy speeds up renal recovery in patients who were diagnosed with drug-induced interstitial nephritis, according to some studies (39). A 42 patients with acute interstitial nephritis in which 26 were given steroid therapy were contrarily studied in one study and 16 patients were not treated in that study (6). No major difference in serum creatinine levels among the two groups of the patients after one, six, and twelve months of regular checkup was observed in the study. To examine the effectiveness of corticosteroid therapy in order to guide clinicians, no trial is obtainable. Providers will be assisted by more observational studies in order to make clinical decisions related to these patients. Till now the approach is totally deployed on the participation and inclination of the provider. In most of the cases, the result of rifampicin-induced acute renal injury is appreciative. Early identification of this condition should be a prime concern. During the early stages of treatment of tuberculosis, to carry out trials on patients with previous exposure to rifampicin for hematuria in order to detect and analyze rifampicin toxicity should be a priority (34). If perceived early, the use of the drug could be discontinued so that the further damage to the patient's renal system could be averted.

Due to side effects profile of corticosteroids, our study provides better hepatorenoprotective effects against rifampicin or isoniazid deleterious impact, moreover, propolis protected liver architecture and histological parameters. A similar action was reported by other studies conducted on rodent's model using rifampicin/isoniazid or melatonin as an oxidant insults. The results confirmed and in agreement with our findings providing protection evidence against deleterious insults (40, 41). The present study recommends expanded study showing the protective effects of propolis on different organ and function.

Conclusion

Propolis blocked the damaging effects of rifampicin and isoniazid and restored normal quasi-equilibrium milieu of kidneys and liver. These positive effects guide physician and healthcare providers to consider propolis as an adjunct therapy for kidney and liver injury.

Acknowledgment

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Conflict of Interest

The authors declare that no conflict of interest exists for this research.

Adherence to Ethical Standards

The study was approved by the Medical Research Ethics Committee in the university of Mosul, the study approval number and date UOM/COM/MREC/2020-2021 (32) on 07/04/2021.

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