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Propolis Mitigates Rifampicin/Isoniazid-induced Lipid-redox and Metabolic Profile in an Experimental Animal Model of Oxidative Stress

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Abstract

BACKGROUND: Adverse drug reactions are the most common cause of drug withdrawal in chronic treatment settings. Tuberculosis (TB) has been considered a recurrent and relapsing disease that needs long-term therapy. Most patients suffer from the adverse effects of TB therapy. Hence, various remedies were used to tackle these adverse effects including antioxidant vitamins, herbal remedies, and others.

AIM: The present intervention study aims to investigate the role of propolis in protecting the animal model against oxidant/antioxidant induced by TB therapy together with the propolis role in modulation of metabolic profile as part of lipid peroxidation context.

METHODS: Serum was collected from rats exposed to rifampicin/isoniazid with or without propolis therapy alongside the control placebo group for comparison.

RESULTS: The results have shown a significant ($p < 0.05$) reduction of malondialdehyde and significant ($p < 0.05$) elevation of total antioxidant status. Lipid profile positively improved indicated by significantly reduced total cholesterol, triglyceride, and elevated high-density lipoprotein.

CONCLUSION: Our study confirmed that propolis provides protection against redox and metabolic derangement induced by rifampicin/isoniazid medications which are in current TB therapy; therefore, we do advise the use of propolis as an adjunct therapy for patients on such medications.

Introduction

In the middle ages and classic times, many bee products have been used for various purposes [1], [2]. These products include propolis, bee wax, royal jelly, honey, and bee pollen is being used for beauty purposes in ancient China [1], [2], [3]. These products are also been used as effective medicines in today's era [1], [2], [3], [4]. The use of such products is also growing in treating cancers [4], neurogenerative diseases [5], [6], cardiovascular diseases [7], and gastrointestinal tract-related disorders [8]. Treatment of wounds and burns can also be performed effectively using bee-related beneficial products [9]. Adverse impacts of oxidative stress regarding the etiology of various diseases could also be encountered by the use of bee products that act as an effective source of natural anti-oxidants [10].

Mainly, the anti-oxidant capacity of bee products is accountable to substances having phenolic characters that have the power to rummage for free radicals [11], [12], [13], [14]. Phenolic acids and flavonoids are the two main groups of such compounds [15]. Neoflavonoids, isoflavones, chalcones, anthocyanins, and flavanols, as well as flavanones, are the plant-based derivatives of flavonoids and the best of the subgroups related to flavonoids is those consisting of benzo-gamma pyrone skeleton. Flavonoids are mainly responsible for playing their role in aglycones linked by a "glycosidic bond" with a carbohydrate group. Flavonoids are usually present themselves in the form of glycosides [15], [16], [17]. Phenol groups are also present in flavonoids that pass on them with the anti-radical activity because the radicals established during metabolic processing [16]. The present study tested the function of propolis in attenuating the oxidative stress induced by rifampicin and/or isoniazid.

Materials and Methods

To implement the objectives of the present study, an experimental rat model was used by exposing the rodent to rifampicin and/or isoniazid with the restoration of pro-oxidant status by propolis therapy. A total of

64 rats were used (eight in each group); divided into eight groups in total. Each eight were administered the specific medication and dose on daily basis [negative control group received normal saline, the positive control group received propolis only, rifampicin group and isoniazid group received rifampicin or isoniazid or a combination of them with/without propolis]. The animals were kept in standard conditions adopted by "animal house in the College of Veterinary Medicine/ University of Mosul." The study was registered and approved by College of Medicine/University of Mosul [approval letter UOM/COM/MREC/20-21(37)]. The medications were purchased from local community pharmacy; isoniazid (INH, KOCAK FARMA), rifampicin (Sinerdol, Antibiotice), and propolis (Propolis, NOW food company) were used at doses 50 mg/kg/day, 100 mg/kg/day, and 200 mg/kg/day, respectively.

A serum sample is withdrawn from an individual rat before starting any medication administration; a second serum sample has been collected after 8 weeks of continuous drug administration. A schematic illustration describing workflow is provided (Figure 1).

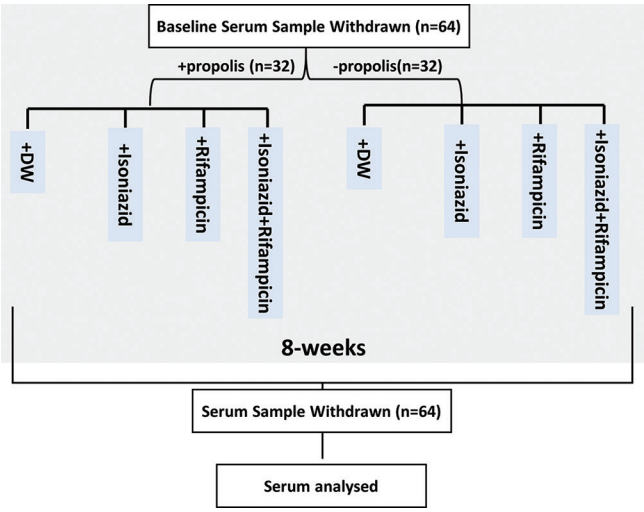

Figure 1: Workflow diagram

The biochemical tests were conducted using commercial kits, including FBS, TC, TG, HDL (Biolabo, France), TAS, and MDA (Elabscience, USA). The measurement of the concentration of glucose, total cholesterol, and triglycerides was conducted according to manufacturer instruction provided in the kit leaflets which through a few steps results in the conversion of the colorless molecules into quinone imine which is a chromogenic compound to be quantified at wavelength 500 nm. Cholesterol in HDL molecules was quantified in the same manner after an initial step of their precipitation through phosphotungstic acid and magnesium chloride. MDA detection based on "ELISA technique", sampled was applied into primed surface plastic with "capture antibody" and after subsequent steps of washing and exposure to detection antibody followed by "enzymatic reaction" using avidin conjugated to "horseradish peroxidase" to be ended by addition of "Tetramethylbenzidine substrate", the analysis ended through exposure to stop solution. TAS measurement based on colorimetric test; the test based on ferrous-ferric conversion followed by the formation of equimolar concentration of colored compound following their reaction with phenanthroline substance.

Results

To identify the role of propolis in the modulation of glycemic control, glucose level and weight were measured in all studied groups and the results were plotted against propolis-free groups. Regarding FBS (mg/dl) 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 are close to the negative control group (102 ± 10.7); except the propolis-treated positive control group has shown significant ($p < 0.05$) reduction (FBS = 94.8 ± 5.2) compared to before starting the propolis therapy (Figure 2a). The weight has been measured as an additional parameter reflecting the health status of the experimental animals. The weight (g) results have shown 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 are close to the control group (212.9 ± 28.1). On the other hand, all propolis-treated groups have shown significantly ($p < 0.001$) higher weight gain compared to parallel propolis-free groups and the level was highest in the propolis-treated positive control group (327.9 ± 31.1) (Figure 2b).

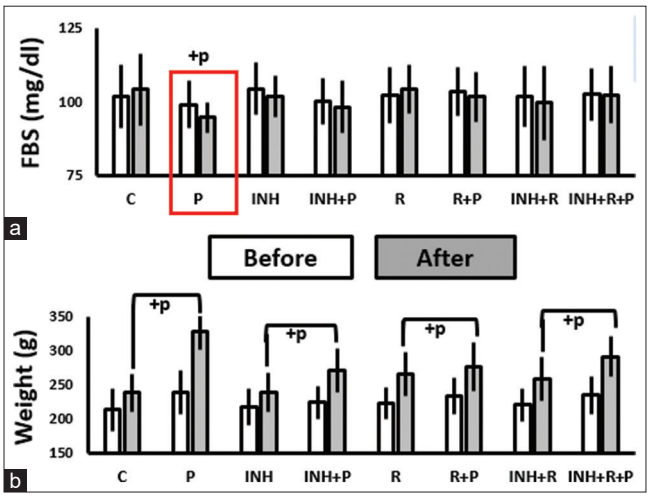

Figure 2: Propolis induced weight gain in the studied groups with no effects on FBS. Rat weight (g) and FBS (mg/dl) were measured before and after propolis therapy in all studied groups. Data expressed as mean ± SD. +p < 0.05 significantly higher in propolis group as a compared propolis-free group. FBS: Fasting blood sugar, C: Control, p: propolis, INH: isoniazid, R: rifampicin

To identify the role of propolis in the modulation of redox status, TAS and MDA concentrations were

measured in all studied groups and the results were plotted against propolis-free groups. Regarding TAS (mM) 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 are close to the negative control group (1.45 ± 0.13) (Figure 3a). The positive control propolis-treated group showed significantly higher TAS levels compared to the control negative propolis free group. On the other hand, TAS levels were significantly reduced in propolis-free experimental animals following their exposure to either INH or rifampicin or a combination of them reaching a level down to (0.68 ± 0.16). However, TAS levels were significantly elevated in propolis-treated experimental animals following their exposure to either INH or rifampicin or a combination of them reaching a level up to (1.74 ± 0.16) (Figure 3a).

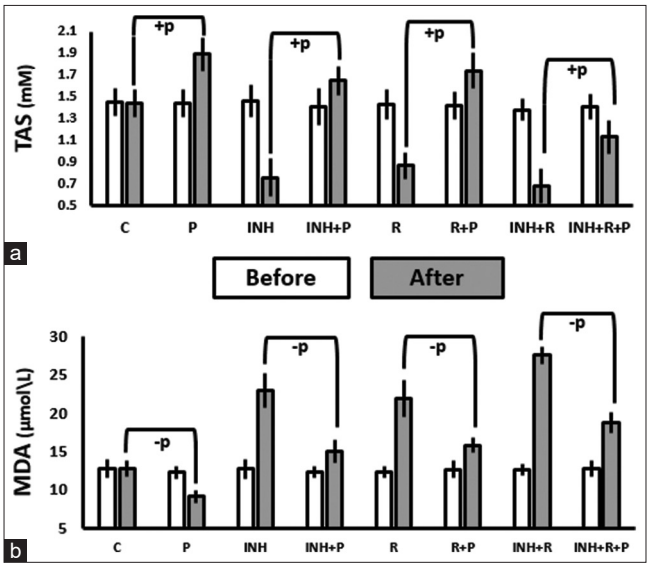

Figure 3: Propolis improved redox status in all studied groups. Serum TAS and MDA were measured before and after propolis therapy in all studied groups. Data expressed as mean ± SD. +p < 0.05 significantly higher in propolis group as a compared propolis-free group. -p<0.05 significantly higher in the propolis-free group as compared to the propolis-treated group. C: control, P: propolis, INH: isoniazid, R: rifampicin. TAS: total antioxidant status, MDA: malondiadehyde

Regarding MDA (μmol/L) 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 are close to the negative control group (12.86 ± 1.18) (Figure 3b). The positive control propolis-treated group showed a significantly lower MDA level compared to the control negative propolis-free group. On the other hand, MDA levels were significantly elevated in propolis-free experimental animals following their exposure to either INH or rifampicin or a combination of them reaching a level up to (27.56 ± 1.07). However, MDA levels were significantly reduced in propolis-treated experimental animals following their exposure to either INH or rifampicin or a combination of them reaching a level down to (15.01 ± 1.53) (Figure 3b).

Regarding TG, TC, and LDL (mg/dl) 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 are close to the negative control group (TG = 119.6 ± 5.4, TC = 121 ± 7.9, and LDL = 47.55 ± 6.62) (Figure 4a, b and d). The positive control propolis-treated group showed significantly lower TG, TC, and LDL levels compared to the control negative propolis-free group. On the other hand, TG, TC, and LDL levels were significantly elevated in propolis-free experimental animals following their exposure to either INH or rifampicin or a combination of them reaching to a level up to (TG = 134.8 ± 8.4, TC = 132.7 ± 4.4, and LDL = 66.98 ± 4.16). However, TG, TC, and LDL levels were significantly reduced in propolis-treated experimental animals following their exposure to either INH or rifampicin or a combination of them reaching to a level down to (TG = 116.9 ± 7, TC = 116.5 ± 7.4, and LDL = 50.21 ± 6.83) (Figure 4a, b and d).

Regarding HDL (mg/dl) 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 are close to the negative control group (49.51 ± 1.98) (Figure 4c). Positive control propolis-treated group showed non-significantly HDL level compared to control negative propolis free group. On the other hand, HDL levels were significantly reduced in propolis-free experimental animals following their exposure to either INH or rifampicin or a combination of them reaching a level down to (38.73 ± 1.3). However, HDL levels were significantly elevated in propolis-treated experimental animals following their exposure to either INH or rifampicin or a combination of them reaching a level up to (42.69±3.07) (Figure 4c).

Discussion

Propolis has significantly inhibited the oxidative damage induced by vitiated insult (rifampicin and isoniazid). These deleterious action has been confirmed through the measuring of TAS and MDA. Rifampicin and isoniazid, in combination or alone, have significantly induced oxidative stress status revealed by significant elevation of MDA and reduction of TAS. When these insults were applied in combination with propolis, the defective oxidation disappeared indicated by a significant elevation of TAS and a significant reduction in MDA. Correspondingly, these actions were positively reflected on the lipid profile, that is, propolis has significantly interfered with the elevated lipid profile induced by rifampicin or isoniazid on a combination of them.

The antioxidant properties of propolis have been confirmed in different *in vitro* laboratory

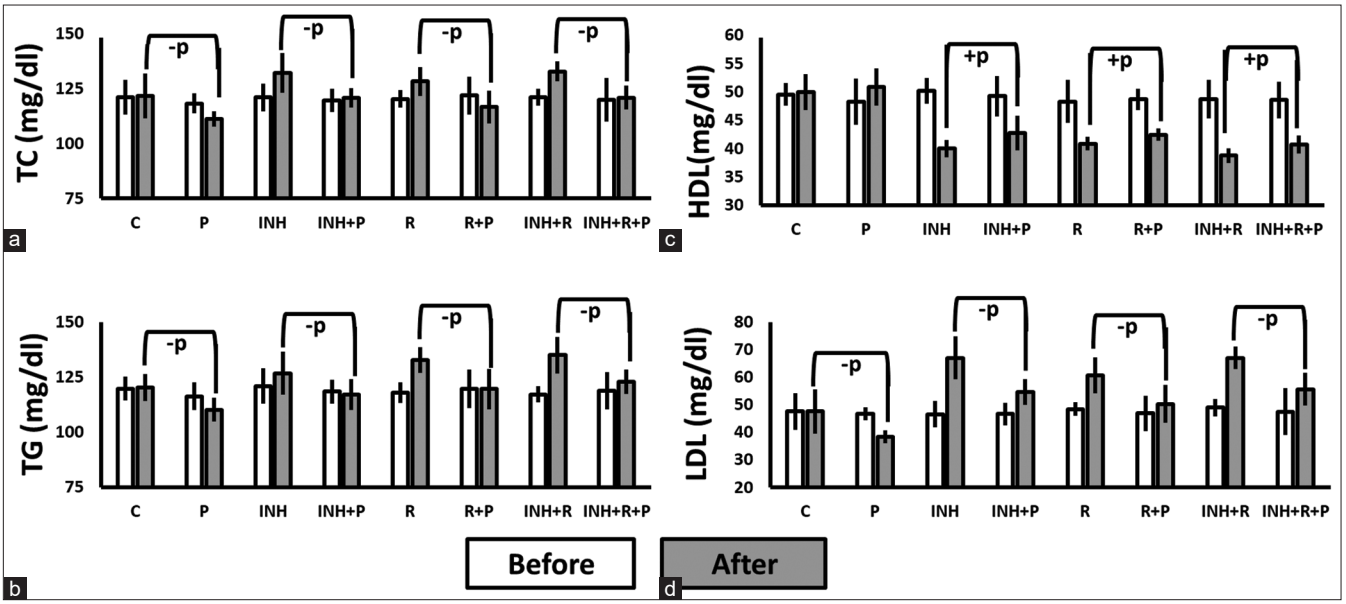

Figure 4: Propolis improved lipid profile in all studied groups. Serum TC, TG, HDL, and LDL were measured before and after propolis therapy in all studied groups. Data expressed as mean ± SD. +p < 0.05 significantly higher in propolis group as a compared propolis-free group. –p < 0.05 significantly higher in the propolis-free group as compared to the propolis-treated group. C: Control, p: propolis, INH: isoniazid, R: Rifampicin. TC: Total cholesterol, TG: Triglycerides, HDL: High density lipoprotein, and LDL: Low density lipoprotein

studies. Different methods have been used in understanding the capacities and properties of propolis including DPPH, ABTS+, FRAP, and ORAC3, [18], [19], [20], [21], [22], [23], [24], [25]. The impacts of the oral administration of propolis solution, on the oxidative status and lipid profile in a human population in Chile have been evaluated by Mujica *et al*. [26]. A decline in the quantity of thiobarbituric acid reactive substances and gain in decreased glutathione (GSH) level compared to the baseline have been examined in propolis supplementation. These thiobarbituric acid reactive substances include TBARS and lipid peroxidation-derived elements. In the propolis supplemented group, total changes of both the studied frameworks were notably higher than those examined in the placebo group. Following propolis supplementation, again in the HDL concentration compared to the initial values was examined and evaluated. Positive impacts on oxidative status and the improvement of HDL of propolis supplementation have been observed by the researchers. It is also observed to be proven beneficial in the reduction in the risk of cardiovascular problems. Positive antioxidant effects obtained on antioxidant enzymes, and a lipid peroxidation marker—malondialdehyde (MDA), using 30-day supplementation with the powdered propolis extract that is available in the market (a total daily dose of flavonoids was 48.75 mg) in healthy individuals was examined by Jasprica *et al*. [27].

After 15 days of the propolis treatment process, a 23.2% decline in MDA level was examined. A 20.9% gain in SOD activity after 30 days of propolis treatment was observed. However, MDA concentration was observed as same as that of baseline value at the end of the treatment process, surprisingly. As such no negative or positive impact on any of the studied parameters in women (n = 15) was observed as a result of the propolis treatment. The impacts of propolis were observed both time and gender-dependent in conclusion by the authors as the result of their studies. A possibility of the existence of only the transitory effect of propolis ingestion on lipid peroxidation has been suggested by the authors.

The impact of propolis on lipid profile has been confirmed *in vitro* cell culture by Fang *et al.,* using “human umbilical vein endothelial cells (HUVECs)”. The study confirmed that oxidized LDL, MDA, reactive oxygen species generation, and nicotinamide adenine dinucleotide oxidase activation were reduced [28]. An action that has been further confirmed in a study conducted by Tian *et al*. [29], who has reported propolis provided protection against macrophage apoptosis induced by ox-LDL. Glucose-induced oxidative vascular damage has been attenuated in rat aorta using a propolis-based *in vitro* model [30].

The positive effects of propolis in reducing lipid and oxidative stress were comparable to pharmacological interventions of statins and antioxidant vitamins or micronutrients in the current use [31], [32], [33], [34], [35], [36]. The exact molecular mechanism is incompletely understood. However, in the study conducted by Zhao *et al*. [37] on patients with “Type 2 diabetes mellitus” (T2DM), a study examines the impacts of Brazilian green propolis supplementation regarding antioxidant status. A gain in serum levels of GSH and total polyphenols and decrease in serum carbonyls (protein oxidation markers) with that of lactate dehydrogenase activity was found to be linked by propolis administration. Furthermore, a decreased TNF-α serum level and importantly increased IL-1β

and IL-6 sera levels were found in the Brazilian green propolis group. Hence, "serum glucose, glycosylated hemoglobin, insulin, aldose reductase, and adiponectin" levels were not found to be affected by propolis treatment. Only the oxidative stress in "Type 2 diabetic patients" is affected by the propolis treatment according to the results of the above-mentioned studies. However, there is no such effect that was observed related to the parameters of diabetes.

Conclusion

In the present study, we demonstrated a model of oxidative stress using commonly indicated TB-therapy drugs (rifampicin and isoniazid), we did found that TB therapy impaired oxidative stress and lipid profile in a rat model and propolis protected against the deleterious damage of TB therapy whether as a monotherapy or in combination. Our recommendation is to conduct clinical trial in human and explore the protective mechanism of propolis investigated in this study.

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