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Original Research Article

Can Sildenafil Citrate Be a Game Changer in the Management of Tuberculosis? A Food for Thought?

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Abstract: *Isoniazid (INH) and Rifampicin (RIF) are cornerstone drugs in tuberculosis therapy but are known to cause hepatotoxicity. Sildenafil citrate, a phosphodiesterase-5 inhibitor, has shown potential antioxidant and anti-inflammatory properties, yet its hepatoprotective effects have not been extensively evaluated.* ***Objective:*** *To investigate the biochemical changes induced by combined INH-RIF therapy and assess the potential hepatoprotective effects of sildenafil treatment in a murine model.* ***Methods:*** *This randomized experimental study involved 21 Swiss albino mice (25–35 g), divided into three groups (n=7 each) using simple balloting. Group C (control) received 0.4 mL/kg normal saline intraperitoneally for 21 days. Group R (INH-RIF) was administered isoniazid and rifampicin (50 mg/kg each) intraperitoneally, daily for 21 days. Group S (INH-RIF + Sildenafil) received the same INH-RIF regimen with concurrent oral sildenafil (10 mg/kg) via gastric gavage. At the end of treatment, serum liver function tests (LFTs) were analyzed. Data were processed using descriptive statistics; inter-group differences were assessed using appropriate statistical tests with significance set at $p < 0.05$.* ***Results:*** *Group R exhibited significant elevation in serum hepatic enzymes indicating hepatotoxicity. Group S showed marked improvement in LFT parameters compared to Group R, suggesting attenuation of hepatotoxicity. Group C maintained normal hepatic profiles. Sildenafil administration resulted in a statistically significant reduction in biochemical markers of liver injury.* ***Conclusion:*** *Sildenafil citrate demonstrates a protective role against INH-RIF-induced hepatotoxicity, supporting its potential therapeutic use in minimizing anti-tuberculous drug-induced liver injury.*

Keywords: Hepatotoxicity; INH-RIF; oxidative stress; sildenafil citrate; Biochemical changes

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Introduction

In Pakistan, as well as other countries, tuberculosis continues to be one of the most common diseases and fatalities (1). The WHO continues to see isoniazid-rifampicin combination therapy as a fundamental component of anti-tubercular treatment (2). Mycolic acid synthesis is inhibited when INH, given in an inactive state, is activated by the KatG catalase-peroxidase enzyme in Mycobacterium tuberculosis. INH's toxic effects are mediated by its metabolites, Hydrazine and Acetyl Hydrazine, which are generated by Acetyltransferase and then undergo oxidation by Cytochrome p450 to yield hepatotoxic metabolites (3-4). Hyperbilirubinemia without conjugation is brought on by RIF. Combining RIF with INH causes hazardous metabolites to be produced more quickly, which leads to pathological alterations in the mouse liver (3).

Antitubercular drug-induced hepatotoxicity varies between 2 28% and 11% of patients, according to the research. Asymptomatic increase of liver enzymes occurs in 20% of individuals taking the combination treatment. Raised levels of the enzymes alanine aminotransferase (ALT) and aspartate transaminase (AST) have been identified as indicators of hepatotoxicity in studies. A spike in ALT and AST readings that is three to four times the usual range, along with symptoms of acute liver poisoning, including nausea, vomiting, abdominal discomfort, fatigue, and jaundice, is observed (5-6). In a qualitative histological animal research using INH/RIF, hepatic histologic changes were discovered (4-7). Hepatocytes were enlarged and showed vacuolization and an excess of eosinophilic cytoplasm. The sinusoids were dilated, and the lumen contained a significant amount of erythrocytes. Congestion and dilation were visible in the central veins. In another study, rats with portal triaditis and micro-vascular fat deposition in the liver were used to explore the mechanism of liver injury owing to INH-RIF combination therapy (8).

A decrease in the levels of glutathione, Superoxide dismutase, glutathione peroxidase, and glutathione-S-transferases indicated increased oxidative stress in INH-RIF therapy, according to the literature. The aetiology was suggested by both the changed antioxidant enzyme profile and the elevated lipid peroxidation. One of the deadliest side effects of combination therapy is the potential for fulminant hepatic failure (9).

Phosphodiesterase inhibitor sildenafil citrate was initially licensed for the treatment of pulmonary hypertension and erectile dysfunction.(10) Sildenafil inhibits oxidative stress and reduces inflammatory alterations, according to recent literature.(11) Both abnormal liver function tests and thioacetamide-induced liver fibrosis have been linked to Sildenafil's hepato-protective effects (12). When sildenafil and paracetamol were given to Wister rats, one of the known hepatotoxic medications, it was discovered that phosphodiesterase 5 inhibition has a protective effect against paracetamol-induced liver damage (13). Improvement in renal function tests (RFTs) and reversal of histological abnormalities in rat kidneys were two ways that sildenafil's protective role in cisplatin-induced nephrotoxicity was demonstrated in a different study linked to this one by Ayman et al. (14). Sildenafil has been shown to play a significant protective role in oxidative stress-related cardiac, lung, and kidney injuries, but there is little information on its role in liver injury from a biochemical and histological perspective. As a result, this experimental study in a mouse model was created to investigate the hepatoprotective role of sildenafil in the presence of combined INH-RIF therapy. We aimed to study the biochemical changes induced by combined INH-RIF therapy and the protective effect of sildenafil treatment.

Methodology

After review and approval by the Graduate Study Committee, the approval of the proposed research project was taken from the Advanced Study and Research Board, Khyber Medical University vide notification no 1126 dated 31/12/2019, Anatomy department, Khyber Girls Medical College, Peshawar in collaboration with Pakistan council of scientific and industrial research laboratories PCSIR Peshawar. The total duration of the study was six months after approval from ASRB.

The Pakistan Council of Scientific and Industrial Research Laboratories PCSIR Peshawar, collaborated with the Anatomy Department of Khyber Girls Medical College, Peshawar, to carry out this study. The trial lasted for six months in total. Thirty-one healthy male albino mice were purchased from the Veterinary and Research Laboratories in Khyber Pakhtunkhwa, Peshawar, seven mice in each group, of 6–8 weeks. Using the formula E = Total Animals Total Groups, the sample size was determined. E's value should be between 10 and 20, where E is the degree of freedom. So, E = 21 − 3 =18. The attrition formula was used to keep the extra 10 mice as a reserve. An animal experiment was used in this investigation. By using the balloting approach, simple random sampling was carried out into three different groups. Mice between 6 and 8 weeks old weighing 25 and 30 grams were enrolled, but inert and malformed mice were rejected. The mice, which weighed 25–35 g and were kept in PCSIR's animal house, were acquired from Veterinary Research Laboratories in Peshawar. To help them acclimatise, they were kept in a 12-hour light, 12-hour dark cycle at a temperature of 23 2°C for a week. Each group of mice had a unique number. By worldwide standards for studying medications in animals, the dosage was standardised. The mice underwent a general physical examination (GPE) before the start of the study to make sure they were all healthy and free of any obvious deformities. Before the start of the experiment and before the killing of the mice, all the animals were weighed using an electronic animal scale. All mouse weights were kept track of.

The Khyber Girls Medical College's Anatomy Department calculated and prepared solutions for two drug classes, INH-RIF and Sildenafil citrate.

The groups were as follows:

Group C: The Control group (n=7) mice were administered 04ml of saline per kg of body weight daily intraperitoneal for 21 days.

Group R: (n=7). In group (R), rifampicin (50 mg/kg) and isoniazid (50 mg/kg), dissolved in 4 ml/ kg isotonic saline, were administered intraperitoneally (i.p.) daily for 21 days.

Group S: (n=7). In group(S), 10mg/kg sildenafil was given orally by gastric gavage daily along with the intraperitoneal injection of INH-RIF (50 mg/kg each) for 21 days. All the drugs were supplied by the authorized suppliers as mentioned in Table 1.

Animals were culled on day 21. Anaesthesia was administered by chloroform-soaked cotton, placed in a 50 ml conical plastic tube. All the rats were euthanized one by one, gently and humanely, by using the drop jar method according to the American Veterinary Medical Association (AVMA) guidelines. Depth of anesthesia for the surgical procedure was assessed by lack of response to toe pinch. Subject to mouse response during sampling, maintenance anesthesia was given by chloroform-soaked cotton, placed in a 50 ml conical plastic tube with the end placed on the mouse's nostril. Closed ventral approach was used for terminal sampling by cardiac puncture with the mouse in a dorsal recumbent position. Heart was approached with 22-23 gauge needles under the sternum and towards the chin, and 0.5-1.5 ml of blood was gradually withdrawn with a 1 ml syringe. Samples were taken to the Clinical Pathology Laboratory, where they were centrifuged at 4000 revolutions/min for ten minutes to separate the serum for the assessment of ALP, AST, and Bilirubin. The summary of the study design is shown in Figure 1.

Figure 1 Summary of study design

Serum alanine aminotransferase was measured by the IFCC-UV kinetic method. Commercially available kit (Liquick Cor-ALAT, PZ Cormay, Poland) containing Tris pH (7.5) (100mmol/L), L-Alanine (500mmol/L/), 2 oxoglutarate (15mmol/L), LDH (>36.7µkat/L), NADH (0.18mmol/L) was used. Levels of alkaline phosphatase enzyme (ALP) were measured by an Optimized standard calorimetric method according to the recommendations of the Deutsche Gesellschaft fur Klinische Chemie. Commercially available kit (ALP, Linear Chemicals, Spain) containing the following reagents, Buffer (D.H.E.A) 1.25mol/L, Magnesium chloride 0.6mmol/L, 4-NPP 50mmol/L was used. Assessment of total bilirubin levels was done by the colorimetric assay kit

Table 1. Details of administered anti-TB drugs

Chemical	Physical state	Strength	Supplier	Use	Dose
Saline	Solution	500ml	Otsuka	Group C	4ml/kg
Sildenafil	Tablets	50mg	Pfizer	Group S	10mg/kg
INH	Tablets	300mg	TB control board	Group R Group S	50mg/kg
RIF	Tablets	300mg	TB control board	Group R Group S	50mg/kg

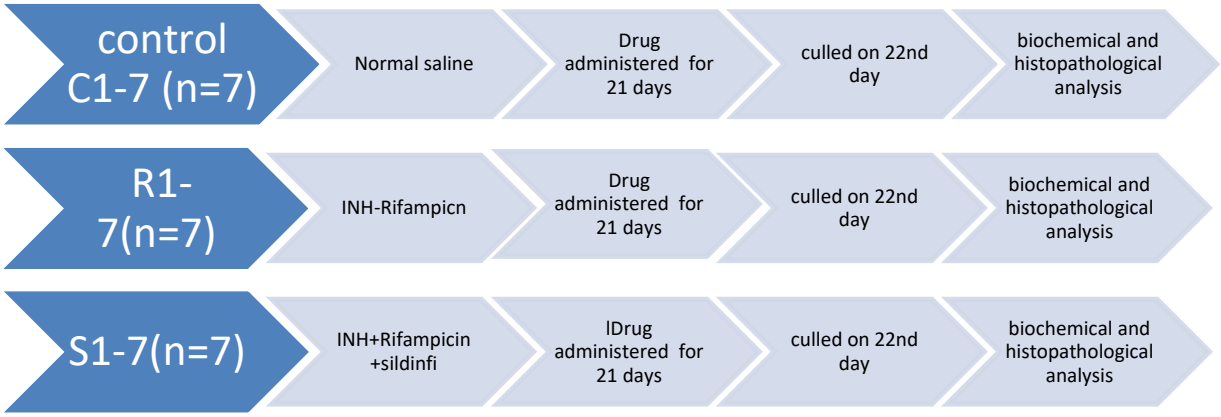

Figure 2.1summary Of Study Design

Results

General observation of study mice:
All of the mice in groups C, R, and S were very active and responded quickly to touch stimuli before the research study began, however after 21 days, the mice in group R were responding more slowly to touch stimuli than the other two groups, C and S.Weight of mice before and after experiment:
The mean weight of mice before and after the experiment was calculated, and t t-test was applied. Table 2
There were no statistically significant changes in weights before and after treatment in any of the three groups (Df=6, P<0.05, 2-tailed) as shown in Table 2. When the Tukey post hoc test was applied, there was no significant weight change between groups C, R, and S. Table 2
Biochemical Parameters (BILIRUBIN, ALT, ALP)
The mean of all three biochemical parameters, Bilirubin, ALT, and AST was calculated. There was a sharp increase in AST and ALP in group R as compared to the control group C and group S, whereas there was no significant change in bilirubin level in all three groups, as shown in Figure 2.
In order to test the alternative hypothesis that Sildenafil citrate may have a protective effect upon biochemical as well as histomorphological changes in mice liver induced by INH-RIF, a between-groups and within-groups one-way ANOVA test was applied, showing no variance for levels of Bilirubin, F 1.163, P=0.335. For other variables like Alanine transaminase, alkaline phosphatase, a statistically significant degree of variance was found, having a P value of 0, 000, 0.000, respectively, as shown in Table 3. To evaluate the nature of differences between means of three groups, the statistically significant ANOVA was followed by a Post hoc test showing a significant increase in the levels of ALT, ALP, weight of liver and Total Knodellar score in R group as compare to values in control group C having P values of 0.00,0.000 respectively. There was no statistically significant difference between group C and S for ALT, ALP, having p>5, thus proving the alternate hypothesis that Sildenafil citrate has a protective role in INH-Rifampicin induced changes in the biochemical parameters of mice liver, as shown in Table 3.

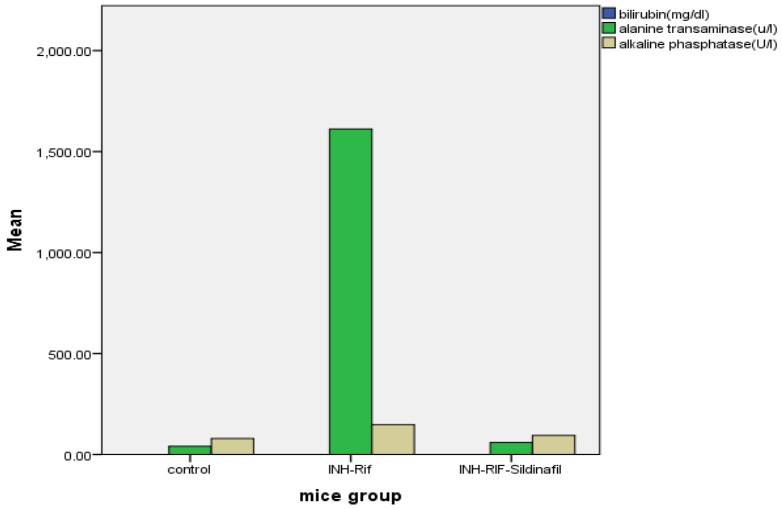

Fig 1.2 Bar chart shows mean values with 2 degree standard deviation of biochemical parameters of mouse liver in group C,R,S

Table 2. Mean weight of mice in groups C, R, and S

Treatments(n)	Mortality	Body weight before treatment	Body weight after treatment	Paired sample test	Anova/Post hoc tukey test
Control	0/7	28.7±2gm	28.1±2gm	0.231	C=R R=S C=S
INH-Rifampicin	0/7	27.5±2gm	27.1±1gm	0.289	
INH-Rifampicin –Sildenafil	0/7	28.7±2gm	28.1±3gm	0.231	

Paired T test P0≥.05 Post hoc Tukey's P≥0.05

Table 3 Inferential statistical group comparison for quantitative biochemical parameters, weight of the liver of the mouse subgroups for analysis of study objectives

		Overall group comparisons by one-way ANOVA	Pairwise significant comparisons Post hoc Tukey test
alanine transaminase(u/l)	Between Groups	.000	C ↔ R
	Within Groups		R ↔ S
	Total		C = S
alkaline phasphatase(U/l)	Between Groups	.000	C ↔ R
	Within Groups		R ↔ S
	Total		C = S
weight of liver (g)	Between Groups	.034	C ↔ R
	Within Groups		R ↔ S
	Total		C = S

↔Shows p ≤ 0.05 whereas (=) shows p > 0.05

Discussion

The centre piece of our research study was that INH_RIF has established hepatotoxic effects, and Sildenafil citrate has antioxidant properties, which proved to be hepatoprotective against the toxic effects.

Every drug has its manifestations in the body, which appear either in the form of biochemical changes at the enzymatic level or histopathological changes at the tissue level. Most of the drugs are excreted either through the hepatic pathway or the renal pathway, which is why the adverse manifestations first of all appear either in the form of abnormal rise in hepatic enzymes like ALP, bilirubin, and ALT, or deranged Renal function tests (RFTs). Derangement in LFTs is always the tip of the Iceberg, representing histological changes at the cellular level at the bottom.

Oxidative stress is one of the documented pathways of drug-induced hepatotoxicity in the literature. Additionally, diets and medications with antioxidant characteristics both play a hepatoprotective role in reducing the harmful effects of medications (15- 16).

One benchmark technique for evaluating the toxicity of a certain medicine is body weight. No discernible difference in body weights, before or after therapy, was found in our investigation. In a study on INH-Rifampicin by Ravinder et al (17). Garlic was given as a hepatoprotective agent, and a hepatotoxic model was created by injecting 50mg/kg INH- INH-Rifampicin. The results showed no differences between the three groups. In another study by Ravinder Pal et al (18). Although carotenoids were seen to have an impact on INH-rifampicin hepatotoxicity, there was no discernible shift in body weights. Our findings generally agree with the previous research.

In clinical practice, when a patient with tuberculosis is started on antitubercular therapy, first of all base baseline liver function tests are checked as hepatotoxicity is one of the known adverse effects of the antitubercular therapy. In our study there was no significant change in the levels of bilirubin in any of the three groups whereas there was a significant increase in AST and ALP levels In group R as compared to control group whereas again there was a significant decrease in Sildenafil administered group S in comparison to group R. International literature shows increase in levels of Bilirubin which is in contrast to our results whereas the significant increase in levels of the AST and ALP are in line with our results, moreover when Spirulina Maxima was administered which is one of a potent anti-oxidant like Sildenafil citerate there was significant decrease in the AST and ALP levels which is again similar to our results (19).

In another research article where the protective effects of metallotheonin in the body are checked against INH-Rifampicin, there was a significant rise in the level of AST and ALP in the mouse group which were administered INH-RFP, in contrast to a significant decrease in the levels of AST and ALP in the metallotheonin positive mouse group, which has established anti-oxidant properties (20).

. In a very detailed research study conducted by Yilin Yang et al (21). The protective effects of Diallyl trisulfide (DATS) were studied against the histomorphological and biochemical effects of INH-RIF. The mice were divided into six groups, and DATS (10mg/kg, 20mg/kg, and 40mg/kg body weight) were administered two hours before administration of INH-RIF (100mg/kg &100mg/kg BW), respectively. The levels of AST, ALP, liver weight, and histological parameters were studied. Similar to our work, co-administration of DATS significantly decreased the rise in liver index and elevation of blood ALT, AST, and Bilirubin levels caused by INH&RFP, in addition to enhancing the hepatocellular structure. Because DATS has an anti-oxidant effect similar to Sildenafil citrate, a noticeable improvement in liver morphology was seen.

One of the key factors in the development and progression of liver injury is the presence of reactive oxygen and nitrogen species. Free radicals are extremely reactive because they have unpaired electrons. These reactive species trigger DNA strand breaks, lipid peroxidation, and ultimately oxidise every molecule in the cell membrane, causing damage to the cell. In a healthy individual, the production of antioxidants and oxidative agents typically coexist in harmony (22).

It is well recognised that several non-toxic plants have opposite effects, such as stabilising membranes, acting as antioxidants, and inhibiting CYP2E1. According to a literature study, liver cell coherence is maintained, and the abnormal level of liver enzymes is controlled by increased superoxide dismutase, catalase, glutathione, and glutathione peroxidase activities, as well as decreased levels of lipid peroxide concentration in tissue (23).

Although the precise mechanism of hepatotoxicity is unknown, lipid peroxidation and oxidative stress are thought to be responsible for INH and RIF-induced damage. These events alter the structure of cell walls, lower glutathione levels, and activate CYP2E1 (22-23). PDEs are crucial in the regulation of both healthy and unhealthy cellular signalling pathways. The PDE5 family inhibition mostly raises cGMP levels because it hydrolyzes cGMP in particular. PDE5 inhibitor sildenafil is primarily used to treat pulmonary hypertension and erectile dysfunction. During ischemia-reperfusion injury, it also triggers protective effects in a number of organs, including the kidneys and lungs (24). These characteristics led to the use of sildenafil as an antioxidant and the observation of its protective effects on the liver. This study opens up new avenues to climb further upon the shoulders of this research, and randomised trials should be done to establish the protective role of Sildenafil in INH-R induced hepatotoxicity. Our limitations in this research study were very small data, and no guidelines could be changed based on this data.

Conclusion

It is concluded that INH and RIF exhibit hepatotoxic potentials as evident from the derangements in hepatic biochemical parameters.

We have also concluded that sildenafil has a hepatoprotective role against INH-RIF-induced hepatotoxicity if administered along with it, as evident by significant improvement in biochemical parameters.

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Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-324-24))

Consent for publication
Approved

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Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

NH
Manuscript drafting, Study Design,
Review of Literature, Data entry, Data analysis, and drafting article.

KF
Conception of Study, Development of Research Methodology Design, Study Design, manuscript review, critical input.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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