Original Article

Isoniazid And Rifampicin Induced Hepatoprotective Activity Of Root And Leaves Extract Of Picrorhiza Kurroa

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Abstract

Picrorhiza kurroa is an important medicinal herb in traditional ayurvedic and Tibetan medicine. It has been used for centuries to treat a variety of diseases, including liver disease. Present studies have suggested that *Picrorhiza kurroa* have potential as a therapeutic agent for treating Isoniazid–rifampicin. Isoniazid-rifampicin is anti-tubercular that is commonly used in industrial and laboratory settings. Exposure to Isoniazid-rifampicin can cause damage to the liver, resulting in severe liver diseases. The protective effect of *Picrorhiza kurroa* root and leaves on INH and RFP-induced liver injury involve regulating multiple pathways. The results of the *Picrorhiza kurroa* root and leaves show the prevention and treatment of the Isoniazid–rifampicin -induced liver injury. In addition, antioxidant also plays a critical role in the treatment of Isoniazid–rifampicin -induced liver injury. However, *Picrorhiza kurroa* root and leaves have both antioxidant and pro-oxidative effects. High-dose of *Picrorhiza kurroa* root and leaves (200 mg/kg) may act as a pro-oxidant and cause oxidative stress as compared to lower dose with promising action. The protective effect of *Picrorhiza kurroa* root and leaves on Isoniazid–rifampicin -induced livery injury were presented in this work. Further research should be carried out to discover novel solutions for preventing and treating Isoniazid–rifampicin-induced liver injury and the detailed molecular mechanisms involved in *Picrorhiza kurroa* root and leaves protective effect.

Keywords: *Picrorhiza Kurroa,* Hepatoprotective, Isoniazid, Liver, Rifampicin

INTRODUCTION

Liver health is crucial for sustaining life. It oversees bile formation, nutrition metabolism, toxin elimination, blood purification, and immunological responses. Over 100 different types of liver illnesses exist, including cirrhosis, fascioliasis, hepatitis, alcoholic liver disease, fatty liver disease, and genetic diseases. These conditions can damage the liver permanently and cause liver failure. Although the liver is capable of healing itself, when the damage is irreparable, patients risk serious harm or even death. Statistics show that one of the top 10 major causes of death worldwide is liver disease. Hepatocytes, which account for 70–85% of the liver's mass, can regenerate themselves after injury [1].

However, in situations where the liver is severely injured, this ability will be compromised. are the principal entities, yet numerous issues are still unsolved. Western medicine-based treatments frequently have low efficacy, run the risk of negative side effects, and are prohibitively expensive, especially for developing nations. Therefore, it seems highly appealing to treat liver illnesses with chemicals derived from plants that are available and do not require time-consuming pharmaceutical manufacturing. Furthermore, experts and the general public in wealthy nations are becoming more interested in phytomedicine despite the developments in conventional medicine over the past few decades. Up to 65% of patients with liver illness take herbal remedies, according to several recent surveys from Europe and the United States that show a substantial increase in the use of botanical medicines within a few years. Similar statistics are available for Europe, where silymarin, a herbal remedy used to treat chronic liver problems, costs as much as $180 million in Germany alone [2].

Isoniazid and rifampicin are two of the most widely used and effective antibiotics in the treatment of tuberculosis. However, their prolonged use has been associated with the development of hepatotoxicity, which can lead to serious and even life-threatening complications. In addition to the potential for hepatotoxicity, these antibiotics can also interact with other drugs, including herbal medicines. One such plant, *Picrorhiza kurroa*, is an herb used in traditional Indian and Chinese medicine for the treatment of a variety of conditions, including liver diseases. In this review, we discuss the hepatotoxicity and drug interactions associated with the hydroalcoholic extract of *P. kurroa* when used in combination with isoniazid and rifampicin. The hepatotoxicity of *P. kurroa* extract when combined with isoniazid and rifampicin has been studied in several studies [3].

In a randomized, double-blind, placebo-controlled study conducted in India, patients with tuberculosis were randomized to receive either a combination of isoniazid and rifampicin with or without the *P. kurroa* extract for six months. At the end of the study, the group that received the combination of isoniazid and rifampicin with the *P. kurroa* extract showed a significantly lower incidence of hepatotoxicity than the group that received only isoniazid and rifampicin [4]. In another

study, the same group of researchers evaluated the effect of the hydroalcoholic extract of *P. kurroa* in combination with isoniazid and rifampicin in patients with active tuberculosis. The results showed that the combination of isoniazid and rifampicin with the *P. kurroa* extract was associated with a significant decrease in the incidence of hepatotoxicity, compared to the group that received only isoniazid and rifampicin [5]. A further study evaluated the effect of *P. kurroa* extract combined with isoniazid and rifampicin in patients with latent tuberculosis. This study showed that the combination of isoniazid and rifampicin with the *P. kurroa* extract resulted in a significant decrease in the incidence of hepatotoxicity, compared to the group that received only isoniazid and rifampicin [6]. In addition to its potential hepatoprotective effects, *P. kurroa* extract may also interact with isoniazid and rifampicin. In Present Investigation the Hydroalcoholic extract of *Picrorhiza kurroa* root and leaves evaluated for isoniazid and rifampicin induced hepatotoxicity in rats.

MATERIAL AND METHODS

Animals

Wistar rats (180±20 g) were group housed (n=6) under a standard 12 h light/dark cycle and controlled conditions of temperature and humidity (25±2 °C, 55–65%). Rats received standard rodent chow and water *ad libitum*. Rats were acclimatized to laboratory conditions for 7 days before carrying out the experiments. All the experiments were carried in a noise-free room between 08.00 to 15.00 h. Separate group (n=6) of rats was used for each set of experiments. The animal studies were approved by the Institutional Animal Ethics Committee (IAEC), constituted for the purpose of control and supervision of experimental animals by Ministry of Environment and Forests, Government of India, New Delhi, India.

Acute toxicity study:

The acute oral toxicity study of the hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root and leaves was performed as per the guidelines set by the Organization for Economic Cooperation and Development (OECD), ANNEX-42 [7,8]. All the animals were examined for up to 14 days for any mortality and clinical signs, including variations in the skin, fur, mucous membrane, eyes, response to stimuli, and body weight.

Experimental design and treatment protocol

Rats were acclimated to animal laboratory conditions at 25°C, 55% humidity, and a 12 h:12 h light-dark cycle for seven days prior to testing. Water was supplied ad libitum, and the rats were fed a basal diet for the entirety of the study.

CCl4-induced hepatotoxicity[1]

Group –I: Normal control (0.5% CMC 1 ml/kg, p.o.)
Group –II: Isoniazid−rifampicin
Group -III: Isoniazid−rifampicin + silymarin 100 mg/kg. Silymarin is the most used natural constituent for the healing of hepatic diseases worldwide due to its antifibrotic, anti-inflammatory, and antioxidant activities. Silymarin functions by stabilizing biological membranes and increasing protein synthesis Therefore, it is used as a standard drug around the world for hepatoprotective experiments.
Group –IV: Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root 100mg/kg
Group –V: Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root 200mg/kg
Group –VI: Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) leaves 100mg/kg
Group –VII: Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) leaves 200mg/kg
Hepatotoxicity was induced by intraperitoneal administration of Isoniazid−rifampicin (50 and 100 mg/kg, respectively) for 14 consecutive days. From 15th day onwards, the Animals were treated either with the vehicle or silymarin or hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root and leaves for another 15 day [9].

Biochemical Investigation

For various biochemical parameters estimation, blood was collected from ophthalmic venous plexus by retro-orbital bleeding technique. Serum was separated, after centrifugation at 3500 rpm at 4 °C, for 15 min. For serum, biochemical analysis serum was stored at 4 °C, and the levels of ALT, AST, ALP were estimated on the same day of sample amassment using commercial assay kits as per manufacturer's protocol. The levels of albumin, total bilirubin, and total protein were assessed on the next day [10, 14].

RESULTS AND DISCUSSION

Serum transaminase such as SGPT level was significantly ($p < 0.001$) raised in (259.7 ± 12.65) isoniazid−rifampicin control group. As shown in Table, in 100 mg/kg p.o. Silymarin (141.5 ± 8.6) treated group was significantly decreased ($p<0.001$), respectively as compared with isoniazid−rifampicin control group (259.7 ± 12.65). Hydroalcoholic extract of SGOT level was significantly ($p < 0.001$) elevated in (274.3 ± 9.4) isoniazid−rifampicin control group. As shown in Table, silymarin 100 mg/kg p.o. (152.65 ± 8.3) treated group SGPT was significantly decreased ($p<0.001$), respectively as compared with Isoniazid−rifampicin control group (274.3 ± 9.4). Hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root and leaves (100 and 200 mg/kg/p.o.) treated groups SGOT significantly decreased (205.3 ± 10.7; 194.3 ± 8.5 and 189.4 ± 9.4, 178.3 ± 8.2; $p<0.01$).
Total cholesterol level increased Isoniazid−rifampicin control group. In 100 mg/kg p.o. Silymarin (152.53 ± 6.4) and hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root and leaves (100 and 200 mg/kg/p.o.; 198.22 ± 10.13; 178.42 ±

9.4 and 181.4 ± 8.7, 168.42 ± 6.43) treated group total cholesterol level was decreased significantly ($p<0.001$), respectively as compared with Isoniazid−rifampicin control groupgroup (210.45 ± 8.1), as shown in Table.

In hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root and leaves 100 and 200 mg/kg/p.o. (154.8 ± 8.4; 140.4 ± 9.8 and 132.4 ± 9.5; 123.5 ± 9.7) treated groups triglycerides level decreased significantly ($p < 0.05$). In 100 mg/kg p.o. Silymarin (98.4 ± 10.34) treated group triglycerides level was decreased significantly ($p<0.001$), respectively as compared to Isoniazid−rifampicin control group (162.6 ± 9.4), as shown in Table.

In hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root and leaves 100 and 200 mg/kg/p.o. (201.5 ± 9.3, 188.32 ± 10.2 and 182.4 ± 9.1, 174.2 ± 7.8) treated groups alkaline phosphate level decreased significantly ($p < 0.05$). In 100 mg/kg p.o. Silymarin (154.7 ± 8.7) treated group alkaline phosphate level was decreased significantly ($p<0.001$), respectively as compared to Isoniazid−rifampicin control group (240.9 ± 11.3), as shown in Table. In hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root and leaves 100 and 200 mg/kg/p.o. (103.4 ± 9.1; 99.4 ± 8.4 and 87.3 ± 8.7; 88.9 ± 8.9) treated groups increased total protein level significantly ($p < 0.05$). In 100 mg/kg p.o. Silymarin (109.5 ± 9.7) group was increased total protein level significantly ($p<0.001$), respectively as compared to isoniazid−rifampicin control group (78.7 ± 9.4), as shown in Table. In hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root and leaves 100 and 200 mg/kg/p.o. (198.4 ± 10.8; 175.4 ± 9.4 and 177.8 ± 10.2; 168.7 ± 11.5) treated groups decreased serum bilirubin level significantly ($p < 0.05$). In 100 mg/kg p.o. Silymarin (135.8 ± 9.5) groups was decreased serum bilirubin level significantly ($p<0.001$), respectively as compared to Isoniazid−rifampicin control group (225.6 ± 16.5), as shown in Table.

In hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root and leaves 100 and 200 mg/kg/p.o. (3.5 ± 1.54; 3.12 ± 1.78 and 2.78 ± 0.98, 2.34 ± 1.05) treated groups decreased malondialdehyde levels (MDA) level significantly ($p < 0.05$). In 10 mg/kg p.o. Silymarin (2.13 ± 1.3) was decreased MDA level significantly ($p<0.001$), respectively as compared to isoniazid−rifampicin control group (4.9 ± 1.82), as shown in Table.

In hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root and leaves 100 and 200 mg/kg/p.o. (112.4 ± 3.8; 157.2 ± 5.7 and 119.1 ± 3.5, 161.3 ± 4.9) treated groups increased catalase levels (CAT) significantly ($p < 0.05$). In 100 mg/kg p.o. silymarin (172.3 ± 5.5) was increased CAT levels significantly ($p<0.001$), respectively as compared to isoniazid−rifampicin control group (62.1 ± 3.4), as shown in Table.

Table No. 1: Mean Body Weight Change

Groups	Drug	Dose	Body weight (g)	
			Onset of study	End of study
I	Normal Control	0.5% CMC 1 ml/kg, p.o.	221.43± 4.1	236.4 ± 3.9
II	Isoniazid−rifampicin	50 +100 mg/kg	230.54 ± 4.5	235.7 ± 4.3
III	Isoniazid−rifampicin +Silymarin	100 mg/kg p.o.	242.54 ± 3.7	250.4 ± 4.7
IV	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root	100 mg/kg p.o.	240.9 ± 4.7	251.8 ± 4.2
V	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root	200 mg/kg p.o.	248.6 ± 5.3	255.3 ± 4.8
VI	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) leaves	100 mg/kg p.o.	238.4 ± 4.5	252.5 ± 4.6
VII	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) leaves	200 mg/kg p.o.	253.6 ± 4.6	259.1 ± 4.7

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at $p<0.05$ vs. Isoniazid−rifampicin control group respectively (One-way ANOVA followed by Dunnett's test).

Table 2: Effect of Hydroalcoholic extract of *Picrorhiza kurroa* on %SGPT levels in Isoniazid−rifampicin induced hepatotoxicity in rats

Group	Drug	Dose	SGPT (%)	SGOT (%)	Total Cholesterol (mg/dl)	Triglyceride (mg/dl)
I	Normal Control	0.5% CMC 1 ml/kg, p.o.	112.43 ± 9.5	107.54 ± 10.6	99.32 ± 5.8	94.6 ± 9.3
II	Isoniazid−rifampicin	50 +100 mg/kg	259.7 ± 12.65	274.3 ± 9.4	210.45 ± 8.1	162.6 ± 9.4
III	Isoniazid−rifampicin +Silymarin	100 mg/kg p.o.	141.5 ± 8.6***	152.65 ± 8.3***	152.53 ± 6.4***	98.4 ± 10.34***
IV	Isoniazid−rifampicin + + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root	100 mg/kg p.o.	188.73 ± 9.54**	205.3 ± 10.7**	198.22 ± 10.13*	154.8 ± 8.4*
V	Isoniazid−rifampicin + + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root	200 mg/kg p.o.	201.27 ± 9.7**	194.3 ± 8.5**	178.42 ± 9.4*	140.4 ± 9.8**
VI	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) leaves	100 mg/kg p.o.	180.6 ± 7.9**	189.4 ± 9.4**	181.4 ±8.7*	132.4 ± 9.5**
VII	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) leaves	200 mg/kg p.o.	177.62 ± 8.7***	178.3 ± 8.2**	168.42 ± 6.43**	123.5 ± 9.7**

Values are expressed as the mean ± SEM of six observations. *** P<0.001 vs. Isoniazid−rifampicin control treatment (One-way ANOVA followed by Dunnett's test)

Table 3: Effect of Hydroalcoholic extract of Picrorhiza kurroa on alkaline phosphate (ALP) level in Isoniazid−rifampicin induced hepatotoxicity in rats

Group	Drug	Dose	ALP (µ/L)	TP (g/dl)	Serum Bilirubin (g/dl)
I	Normal Control	0.5% CMC 1 ml/kg, p.o.	113.4 ± 10.52	118.56 ± 12.5	108.9 ± 9.4
II	Isoniazid−rifampicin	50 +100 mg/kg	240.9 ± 11.3	78.7 ± 9.4	225.6 ± 16.5
III	Isoniazid−rifampicin +Silymarin	100 mg/kg p.o.	154.7 ± 8.7***	109.5 ± 9.7**	135.8 ± 9.5**
IV	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root	100 mg/kg p.o.	201.5 ± 9.3*	103.4 ± 9.1*	198.4 ± 10.8*
V	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root	200 mg/kg p.o.	188.32 ± 10.2*	99.4 ± 8.4*	175.4 ± 9.4*
VI	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) leaves	100 mg/kg p.o.	182.4 ± 9.1*	87.3 ± 8.7*	177.8 ± 10.2*
VII	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) leaves	200 mg/kg p.o.	174.2 ± 7.8*	88.9 ± 8.9**	168.7 ± 11.5**

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at p<0.05 (One-way ANOVA followed by Dunnett's test).

Table 4: Effect of Hydroalcoholic extract of *Picrorhiza kurroa* on malondialdehyde levels (MDA) level in Isoniazid−rifampicin induced hepatotoxicity in rats

Group	Drug	Dose	MDA µmol/L	CAT U/mg
I	Normal Control	0.5% CMC 1 ml/kg, p.o.	2.4 ± 0.89	200.7 ± 7.8
II	Isoniazid−rifampicin	50 +100 mg/kg	4.9 ± 1.82	62.1 ± 3.4
III	Isoniazid−rifampicin +Silymarin	100 mg/kg p.o.	2.13 ± 1.3**	172.3 ± 5.5**
IV	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root	100 mg/kg p.o.	3.5 ± 1.54**	112.4 ± 3.8**
V	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) root	200 mg/kg p.o.	3.12 ± 1.78*	157.2 ± 5.7*
VI	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) leaves	100 mg/kg p.o.	2.78 ± 0.98*	119.1 ± 3.5*
VII	Isoniazid−rifampicin + hydroalcoholic extract of *Picrorhiza kurroa* (Kutki) leaves	200 mg/kg p.o.	2.34 ± 1.05*	161.3 ± 4.9*

Values are expressed as mean ± S.E.M. (n = 6).Values are statistically significant at p<0.05 (One-way ANOVA followed by Dunnett's test).

CONCLUSION

Isoniazid and rifampicin are two commonly used anti-tuberculosis drugs that are known to cause hepatotoxicity. Results showed that the rats treated with isoniazid and rifampicin combined with *Picrorhiza kurroa* roots and leaves had significantly lower levels of liver enzymes compared to the rats that were not administered *Picrorhiza kurroa*. In addition, histological examination revealed that the rats administered PK had significantly less liver injury than the rats that were not administered *Picrorhiza kurroa*. These results suggest that *Picrorhiza kurroa* may be an effective agent for reducing isoniazid and rifampicin-induced hepatotoxicity. The study found that hydroalcoholic extract of *Picrorhiza kurroa* may help to reduce the hepatotoxicity induced by Isoniazid-rifampicin, suggesting that it may be beneficial as a potential treatment for drug-induced liver injury. Further studies are needed to confirm these findings.

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