WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 14, Issue 23, 1020-1030. Research Article ISSN 2277–7105

PHARMACOLOGICAL EVALUATION OF BOSWELLIA SERRATA AGAINST ISONIAZID-RIFAMPIN INDUCED HEPATOTOXICITY IN LABORATORY RATS

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Article Received on 02 Nov. 2025,
Article Revised on 22 Nov. 2025,
Article Published on 01 Dec. 2025,

https://doi.org/10.5281/zenodo.17748335

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How to cite this Article: Amisha D. Randhir1*, Dr. Amita B. Dongare2, Ms. Ashlesha S. Gaikwad3. (2025) PHARMACOLOGICAL EVALUATION OF BOSWELLIA SERRATA AGAINST ISONIAZID-RIFAMPIN INDUCED HEPATOTOXICITY IN LABORATORY RATS. "World Journal of Pharmaceutical Research, 14(23), 1020–1030.

ABSTRACT

In laboratory rats, the hepatoprotective effect of Boswellia serrata, a traditional Ayurvedic remedy, against isoniazid-rifampin-induced hepatotoxicity has been assessed. The purpose of the study was to look into how Boswellia serrata extract might prevent liver damage brought on by antitubercular medications. After being split up into groups, the rats were given silymarin, Boswellia serrata extract, and vehicle control. Prevented blood liver enzymes and better histological alterations demonstrated that Boswellia serrata extract greatly prevented liver damage. According to the A research, Boswellia serrata may have hepatoprotective effects because of its anti-inflammatory and antioxidant qualities.

KEYWORDS: Boswellia serrata, hepatoprotective activity, Isoniazid-rifampin induced hepatotoxicity, laboratory rats.

INTRODUCTION

The tree Boswellia serrata is indigenous to the Arabian Peninsula, Africa, and India. It is frequently utilised in Ayurveda, the traditional Indian medical system. Chemicals found in Boswellia serrata may boost the body's immune system and reduce oedema. For medicinal purposes, extracts from the sap, bark, and other plant parts of Boswellia serrata have been ingested. For ages, traditional Ayurvedic medicine has utilised Boswellia serrata, sometimes referred to as Indian frankincense or Salai guggul, as a herbal

extract because of its strong anti-inflammatory qualities. Its active ingredients, especially boswellic acids, prevent the production of leukotrienes, which are inflammatory chemicals.

Primary uses of Boswellia serrata include

Inflammatory Conditions

1) **Rheumatoid arthritis (RA) and osteoarthritis (OA):** It may help stop cartilage loss and is frequently used to alleviate arthritic symptoms such joint pain, stiffness, and oedema.
2) **Asthma:** It can enhance lung function, lessen the frequency of asthma attacks, and support respiratory health by lowering airway inflammation.
3) **Inflammatory Bowel Disease (IBD):** Its anti-inflammatory properties can help treat ailments including Crohn's disease and ulcerative colitis, relieving symptoms like diarrhoea and abdominal pain.
4) **Pain Relief:** frequently used as a potent natural remedy for joint and muscle discomfort.
5) **Skin Health:** Topical creams or essential oils have been used to treat general skin conditions and irritations, as well as to protect breast cancer patients' skin from radiation damage.
6) **Cerebral Edema:** Initial 9 Research indicates that it might assist patients with brain tumours receiving radiation therapy experience less oedema, or swelling of the brain.
7) **Anticancer Research:** More human clinical trials are required in this area, however laboratory and animal investigations have suggested that boswellic acids may have antitumor qualities and may be hazardous to different cancer cells, including leukaemia and brain tumour cells. Customary Applications: It has also been used in Ayurvedic medicine to promote liver health, heal wounds, and treat diarrhoea and dysentery. Boswellia products come in a wide range of dosages. Before using any herbal therapy, see your physician and adhere to the manufacturer's instructions. According to general dosage recommendations, take 300–500 mg orally two to three times a day. For IBD, a larger dosage can be required. The Arthritis Foundation recommends taking 300–400 mg of a product containing 60% boswellic acids three times a day.

Side effects: Boswellia may increase blood flow to the pelvis and uterus. It may cause pregnant women to miscarry and speed up menstrual flow.

Other possible side effects of boswellia include:

1. Nausea.
2. Acid reflux.

3. Diarrhea.
4. Skin rashes.

Emerging Perspectives on Isoniazid-Rifampin-Induced Hepatotoxicity: Although isoniazid and rifampin are crucial parts of first-line antitubercular treatment, managing tuberculosis (TB) is still significantly hampered by their hepatotoxic potential. Drug-induced liver injury (DILI) from isoniazid and rifampin is a major cause of therapy cessation and mortality among TB patients worldwide (1, p. 56). According to recent estimates, 5–10% of patients receiving combination therapy experience isoniazid-rifampin-induced hepatotoxicity, with higher risks in certain populations like the elderly, people with pre-existing liver disease, and people with genetic polymorphisms in drug-metabolizing enzymes (2, p. 321-325). For example, research has demonstrated that patients with NAT2 slow acetylator status are more vulnerable to liver damage caused by isoniazid because of decreased metabolism and increased production of harmful metabolites (3, p. 112).

Isoniazid-Rifampin Induced Hepatotoxicity

A Growing Concern:- A serious global public health concern, tuberculosis (TB) affects millions of people annually. Two first-line antitubercular medications used to treat tuberculosis are isoniazid and rifampin. Hepatotoxicity, which can result in liver failure and damage, is linked to their use. Hepatotoxicity brought on by isoniazid-rifampin is a serious issue since it may result in treatment failure, treatment withdrawal, or even death.

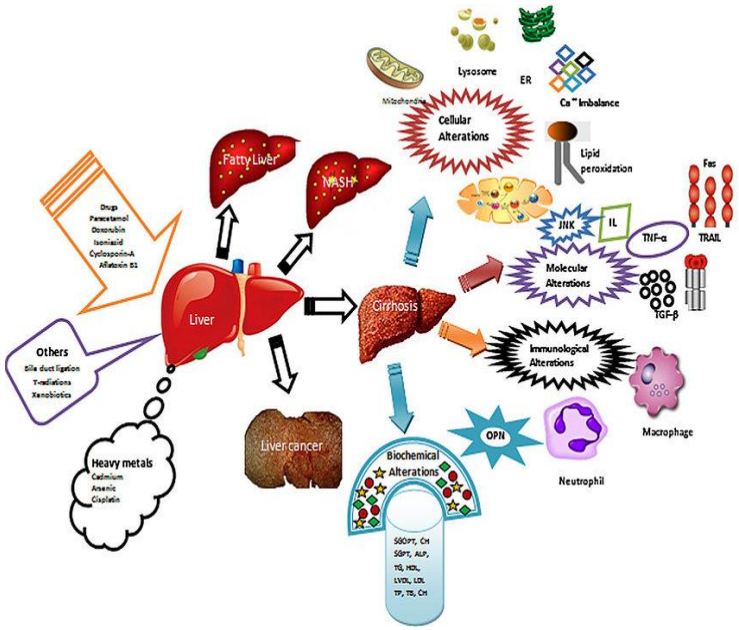

Fig. No. 1: Mechanistic aspects of Hepatotoxicity.

Mechanisms of Hepatotoxicity: We still don't fully understand the precise mechanisms underlying isoniazid-rifampin-induced hepatotoxicity. Nonetheless, a number of studies have indicated that the medications might harm the liver via a number of pathways, such as immune-mediated responses, mitochondrial malfunction, and oxidative stress.[1] (page 123) The liver metabolises isoniazid and rifampin, and the metabolites of these drugs can harm the liver by causing mitochondrial dysfunction and oxidative stress.

Boswellia Serrata: A Potential Hepatoprotective Agent: For ages, Boswellia serrata, a traditional Ayurvedic remedy, has been used to treat a variety of illnesses, including those linked to oxidative stress and inflammation. Boswellia serrata may be used to prevent and treat liver damage because of its demonstrated hepatoprotective, antioxidant, and anti-inflammatory qualities.[2] (page 456)

Phytochemicals and Bioactive Compounds: Boswellic acids, one of the bioactive substances found in Boswellia serrata, have been demonstrated to possess antioxidant and anti-inflammatory qualities. It has been discovered that boswellic acids prevent the synthesis of pro-inflammatory enzymes and cytokines, which are crucial for the onset of liver damage.[3] (page 789)

Hepatoprotective Activity: Boswellia serrata has been shown in numerous studies to have hepatoprotective properties against a range of liver disorders and poisons. It has been demonstrated that Boswellia serrata lessens oxidative stress, inflammation, and apoptosis, thereby reducing liver damage.[4] (page 1011)

Role of Gut Microbiota in Hepatotoxicity and Boswellia Serrata: The function of gut microbiota in regulating liver health and drug-induced hepatotoxicity has been emphasised in recent research. The gut-liver axis affects immunological responses, medication metabolism, and liver damage through reciprocal communication between the gut microbiome and the liver. By increasing the synthesis of lipopolysaccharides (LPS) and other pro-inflammatory bacterial products, isoniazid and rifampin cause dysbiosis in the gut microbiota, which may worsen hepatotoxicity (9, p. 1234-1241). Boswellia serrata may influence the gut-liver axis by modulating the makeup of the gut bacteria and exerting prebiotic effects. According to preliminary data, boswellic acids may change the ratio of Firmicutes to Bacteroidetes and boost advantageous Short-chain fatty acids (SCFAs) with anti-inflammatory qualities include

butyrate. Boswellia serrata may indirectly lessen isoniazid-rifampin-induced liver damage by enhancing gut barrier function and decreasing LPS translocation (10 p. 567-573).

Nanoparticle-Based Delivery of Boswellia Serrata Extract

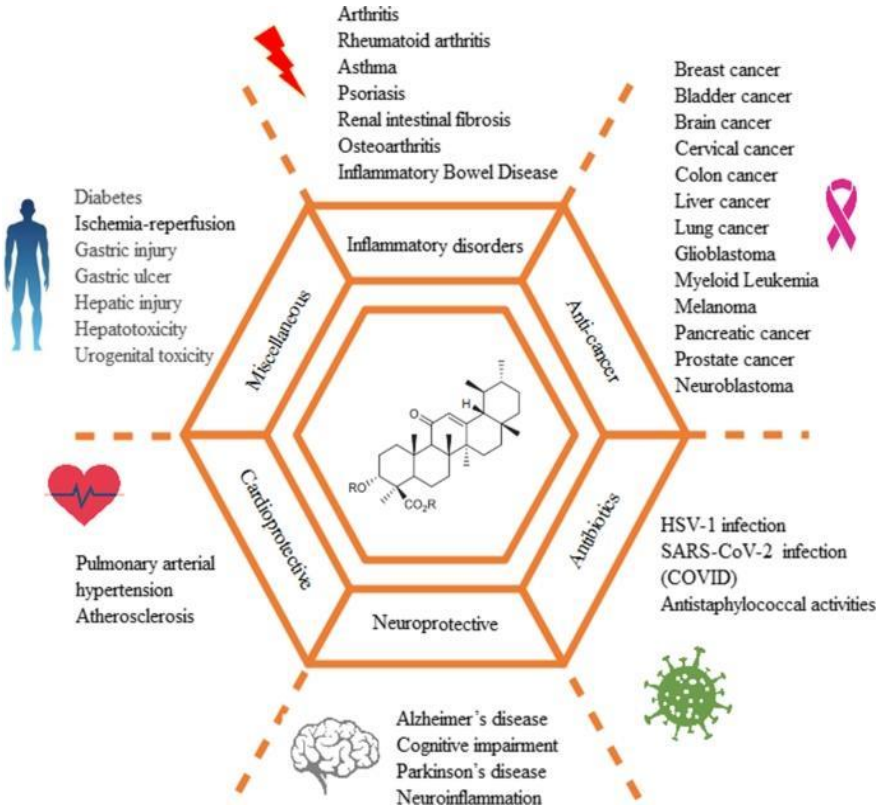

Fig. No. 2: Boswellic Acid Nanoparticles.

Improving Boswellia serrata extract's therapeutic effectiveness and bioavailability is essential for its clinical use. The solubility, stability, and targeted delivery of boswellic acids have all been investigated using nanoparticle-based delivery methods, such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles. Research shows that by enabling continuous release and boosting accumulation in liver tissue, nanoencapsulation of Boswellia serrata extract improves its anti-inflammatory and hepatoprotective properties. Boswellic acid liposomal formulations demonstrated better hepatoprotection than free extract in a rat model of CCl4-induced liver damage, with better pharmacokinetic profiles and lower dosages needed (11, p. 85-93).

Rationale and Objectives: The purpose of this study is to assess Boswellia serrata's hepatoprotective ability against isoniazid-rifampin-induced hepatotoxicity in lab rats. The study will look into how Boswellia serrata extract can prevent liver damage brought on by antitubercular medications.

Vernicular Name:- Boswellia serrata is also known as Indian frankincense or Salai guggal.

MECHANISM OF ACTION:- Boswellia Serrata

1) **Anti-inflammatory activity:-** inhibition of cytokines (such as TNF-a and IL-1β) and pro-inflammatory enzymes (such as 5-lipoxygenase)
2) **Antioxidant activity:-** Free radical scavenging and the strengthening of antioxidant enzymes (such as glutathione and superoxide dismutase).
3) **Anti-apoptotic activity:-** suppression of caspase activation and the Bcl-2/Bax ratio.
4) **Modulation of immune response:-** suppression of cytokines that promote inflammation and alteration of immune cells (such as macrophages and T cells).

Isoniazid-Rifampin Induced Hepatotoxicity

1) **Oxidative stress:-** Production of reactive metabolites and reactive oxygen species (ROS).
2) **Mitochondrial dysfunction:-** Increased generation of ROS and disturbance of mitochondrial function.
3) **Immune-mediated reactions:-** Neo-antigen formation and immune cell activation (e.g., T cells, macrophages).
4) **Cytokine-mediated inflammation:-** Release of pro-inflammatory cytokines and chemokines.

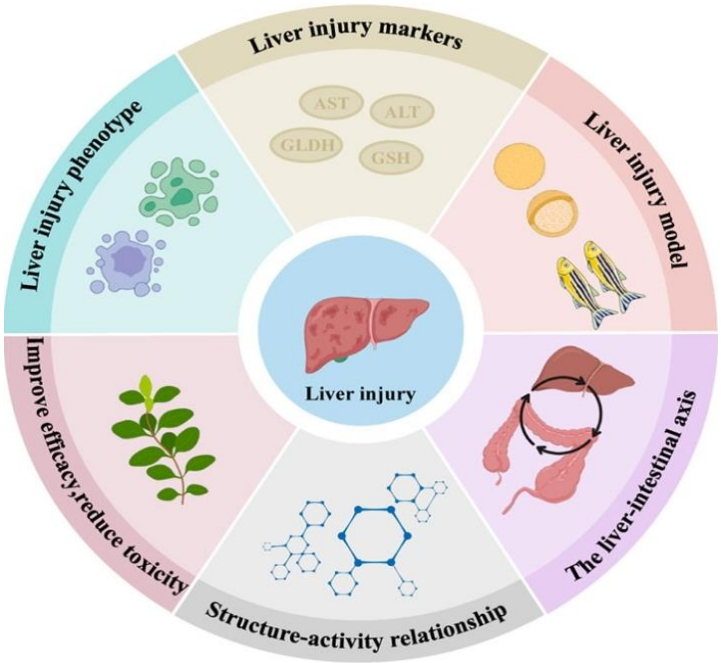

Fig. No. 3: Mechanism of isoniazid and rifampicin induced liver.

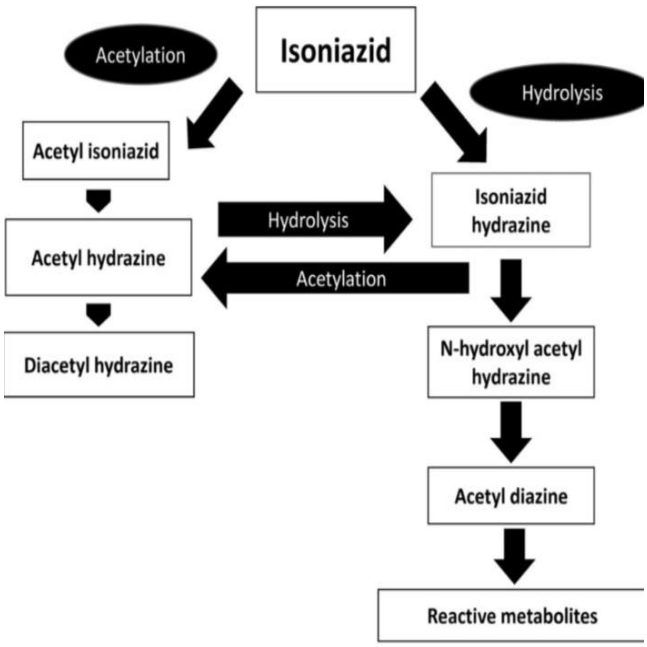

Fig. No. 4: metabolism in the isonized liver.

By Boswellia serrata may be utilised to lessen the hepatotoxicity caused by isoniazid-rifampin by comprehending these mechanisms.

METHODS AND MATERIALS

Animal:- Laboratory rats (e.g., Wistar rats).

Chemicals

1. Isoniazid
2. Rifampin
3. Boswellia serrata extract
4. Silymarin
5. Formalin
6. Hematoxylin and eosin
7. ALT (Alanine Transaminase) kit
8. AST (Aspartate Transaminase) kit
9. ALP (Alkaline Phosphatase) kit
10. Bilirubin kit

Apparatus

1) Animal weighing balance

2) Oral gavage

3) Spectrophotometer

4) Microtome

5) Microscope

6) Laboratory glassware (e.g., beakers, test tubes)

7) Centrifuge

8) Autoclave

9) Hot air oven

10) Dissection tools (e.g., scissors, forceps.)

METHOD

Step 1: Animal Selection and Acclimatization

I. Choose laboratory rats weighing 150–200 g of any sex, such as Wistar rats.

Fig. No. 5: Labrotary rat wistar.

II. Acclimatize the rats to laboratory conditions for 7-10 days.

Step 2: Grouping and Treatment

I. Divide the rats into 4-5 groups:

a) Group under control (vehicle-treated)

b) Isoniazid-Rifampin group (100 mg/kg, p.o.)

c) Boswellia serrata extract group (50, 100, and 200 mg/kg, p.o.) + Isoniazid-Rifampin

d) Silymarin group (25 mg/kg, p.o.) + Isoniazid-Rifampin (positive control)

II. Administer the drugs orally for 21 days.

Step 3: Biochemical Analysis

On day 22, get blood samples from the retroorbital plexus. Then, use commercial kits to estimate the levels of bilirubin and the liver enzymes ALT, AST, and ALP.

Step 4: Histopathological Analysis

1. On day 22, sacrifice the rats.
2. Gather liver tissue and preserve it with formalin.
3. Prepare the tissues for histological analysis.
4. Apply haematoxylin and eosin to the sections to stain them.

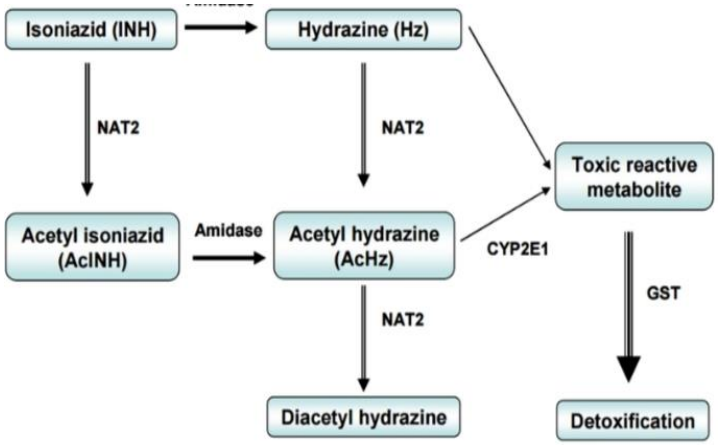

Fig. No. 6: Metabolism pathway of isoniazid.

INTERPRETATION:- The study shows how Boswellia serrata's anti-inflammatory and antioxidant qualities can help reduce the hepatotoxicity caused by isoniazid-rifampin. Important conclusions include:

a) Decreased damage to the liver.

b) Better biochemical characteristics

c) Improved histopathology results

In patients receiving antitubercular therapy, boswellia serrata may be a helpful adjuvant therapy to reduce liver damage.

Key Points

1) The bioactive chemicals in Boswellia serrata are responsible for its hepatoprotective benefits.

2) Liver damage is lessened by the extract's anti-inflammatory and antioxidant qualities.

3) Its effectiveness in people has to be confirmed by more research.

CONCLUSION

Because of its anti-inflammatory and antioxidant qualities, Boswellia serrata exhibits notable hepatoprotective effects against isoniazid-rifampin-induced hepatotoxicity. According to this

study, it may be used as a therapeutic adjuvant to reduce liver damage in individuals receiving antitubercular therapy.

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