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Antioxidant and Hepatoprotective Activities of Pongamia Pinnata (PP) Linn. Leaves on Anti-Tubercular Medicines (Isoniazid & Rifampin) Induced Hepatotoxicity in Wistar Rats

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Abstract---Objectives: -The goal of this study was to see if an aqueous extract of Pongamia Pinnata Linn. (APP) leaves could protect against the hepatotoxicity caused by anti-TB medications (ATM). Methods: -In order to cause hepatotoxicity in rats, anti-tubercular medications were utilised. Silymarin (100 mg/kg p.o.) be present utilised by means of the control medication. For 21 days, an aqueous extract of Pongamia Pinnata Linn. leaves (200 & 400 mg/kg p.o.) was given with anti-TB medicines given one hour before to the aqueous extract. Results: -

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Biomarker enzymes found in the liver are SGPT, SGOT, ALP, Total Bilirubin & total cholesterol remained raised on anti-TB medicines management. The management of aqueous extract of *Pongamia Pinnata* Linn. leaves 200 mg/kg & 400 mg/kg with anti - TB medicines were considerably decreased biomarker enzymes found in the liver. Antioxidant factors like Super Oxide Dismutase (SOD), Glutathione(GSH), Catalase(CAT), Glutathione Peroxidase (GPx)& Glutathione Reductase(GRx) were inhibited and improved ThioBarbituric Acid Reactive Substances (TBARS) points in anti-TB medicines administration then returned these antioxidant points in the management of aqueous extract of *Pongamia Pinnata* Linn. Leaves at a dosage of 200mg/kg & 400mg/kg. Conclusion: - According to the findings of this research, *Pongamia Pinnata* Linn. leaves have a protective consequence against hepatotoxicity caused through anti-TB medicines.

Keywords---antioxidant parameters, anti-TB medicines, hepatoprotective activity, liver biomarkers, *Pongamia pinnata*.

Introduction

The liver is the body's largest glandular structure, considering 1.5kg also accounting intended for around 2-3% of total body weight. By converting and eliminating toxins and wastes, it is responsible for detoxifying the body's toxic substances. The liver performs numerous tasks. Its involvement in the body's metabolism is the most important. In many ways, the liver is more crucial to a healthy metabolism than any other organ [1]. The term "liver disease" refers to a range of diseases that affect the tissues, structures and cells of the human liver. The liver is responsibility for a wide range of vital activities, so there's plenty of scope for anything to go wrong. Inflammation is one of the most common causes of liver illness and it is commonly caused by alcohol abuse, a poor diet, or even malnutrition [2].

Liver damage caused by drugs is a most important public health issue that impacts not just doctors, but also the pharmaceutical business & monitoring bodies. Liver damage caused by drugs accounts for more than 1/2 of acute liver failure, according to the US. The Acute Liver Failure Study Collection, with hepatotoxicity produced by an overdose of acetaminophen (39 percent) and idiosyncratic liver injury caused by other medicines accounting for the other half [3]. Isoniazid, rifampin & pyrazinamide are biotransformed to reactive metabolites capable of attaching to cellular macromolecules and causing toxicity through a multistep mechanism causes ATD-induced hepatotoxicity [4]. Rifampicin is toxic to the liver, as evidenced by its use in the management of tuberculosis & cholestasis [5, 6]. It remained associated by a 5.8 percent occurrence of serious liver injury when combined with pyrazinamide, a 2.6 percent incidence when combined with isoniazid, and a 1.1 percent incidence when taken alone [7].

In the absence of safe and effective liver-protecting medications in "modern" medicine, the search for herbal hepatoprotectives continues. The use of herbal

products as remedies for the treatment of a variety of ailments can be traced back to the Vedic period in India [8]. For hundreds of years, medicinal plants have played an important part in global health as the result healing experiences of generations of indigenous medicine practitioners [9, 10]. As a result, despite significant developments in modern medicine in recent decades, herbal medicines continue to play an essential role in health care [11].

Pongamia Pinnata (Linn.) pierre belonging to the family Fabaceae or Leguminosae is a medium sized glabrous tree called in Hindi as karanja, English as Indian Beech & Tamil as Pongam [12]. *Pongamia Pinnata* has historically been utilised as a folk medicinal herb, predominantly in the Ayurvedha & Siddha systems of Indian medicine [13] for a variety of ailments, including diabetes mellitus [14]. Newly, the usefulness of *P. Pinnata* as a basis of biomedicines, notably antibacterial and therapeutic compounds, has been reported [15]. All constituents of the plant have been employed as a crude medication to treat diarrhea, tumours, painful rheumatic joints wounds piles, abscesses, ulcers, itches, skin illnesses and other conditions [16]. Furthermore, it's widely used as animal feed, green manure, lumber, and fish poison. Because of its insecticidal and nematocidal properties, it has also been demonstrated to be useful in agriculture & environmental controlling [15].

A review of the literature on *Pongamia Pinnata* indicated that it has hepatoprotective & antioxidant properties [17]. It must, however, be scientifically proven. As a result, the current study, headed "Antioxidant and Hepatoprotective activities of *Pongamia Pinnata* Linn. leaves on Isoniazid & Rifampin induced hepatotoxicity" was carried out.

Materials and Procedures

Collection and authentication of plant material

Pongamia Pinnata Linn leaves were obtained in Ananthapuram, Andhra Pradesh. Dr.K.Madhavachetty, Assistant Professor, Department of Botany, Sri Venkateswara University, Tirupati, Andhra Pradesh, India, identified, authenticated & certified the *Pongamia Pinnata* plant.

Plant extract preparation

Using ethanol as a solvent, the air dried up powder remained extracted in a Soxhlet device. The look of colourless solvent now the syphon tube remained used as per the extraction endpoint. Distillation condensed the extract to 34% of its unique capacity.

Studies on acute toxicity

Toxicity that occurs suddenly tests for APP were carried out in accordance with OECD standards 423 [18]. For the investigation, 10 rats were chosen & oral direction of APP at doses of 10, 100, 500 & 2000 mg/kg was assumed at 48-hour intervals. Animals were monitored for variations in food & water consumption,

mortality rates, behavioural changes & body weight in this acute toxic investigation.

Animals

Adult Wistar rats weighing 150 to 250 grammes stood employed & they were bought as of Bangalore-based In vivo Bio sciences. The animals remained kept in hygienic metabolic cages with a constant temperature of ($22 \pm 3^\circ\text{C}$) & a 24hr. light sequence (12hr. light & 12hr. dark). They were given a conventional pellet feed & free access to water. The Raghavendra Institute of Pharmaceutical Education & Research (RIPER) Animal Ethical Committee (IAEC) authorized the protocol (Approval No-07/IAEC/2011).

Protocol of the research

Isoniazid (INH - 27mg/kg,Orally) and Rifampin (R - 40mg/kg,Orally) were employed to induce hepatotoxicity on behalf of 21 days, with Silymarin (100mg/kg,Orally) serving as a control. Using a conversion table based on body surface area, anti-tubercular medication oral doses were calculated from daily human doses.

Methodology for the study

The experimental animals were casually assigned into five groups, respectively with 6 animals & the usage regimen for 21 days was as monitors. Group 1 - Control (Normal saline (NS) 1ml/kg, orally), Group 2 - Toxic control (anti - TB medications - HR, orally), Group 3 - Silymarin (100 mg/kg, orally) + 1 hr. before administration of anti - TB Medicines, Group 4 - APP (200gm/kg, orally) plus 1 hr. before administration of anti - TB medications; Group 5 - APP (400gm/kg, orally) plus 1 hr. earlier administration of anti - TB medicines. On the 22nd day, blood is drawn to define the levels of liver biomarker enzymes. On the similar day, the liver is detached & preserved in a 10% formalin solution used on behalf of the calculation of antioxidant limits, as well as for histological examinations.

Biochemical and anti-oxidative parameter estimation

The Reitman and Frankel approach was used to estimate SGOT & SGPT, whereas the Kind King method was used to estimate ALP. The Jendrassik&Grofs method & the CHOD/POD method were used to calculate total bilirubin and total cholesterol, respectively. Super Oxide Dismutase (SOD) [19], Catalase (CAT) [20], Glutathione (GSH) [21], Glutathione Peroxidase (GPx) [22], Reduced Glutathione (GRx) [23] & lipid peroxidation [24] were used to determine antioxidant parameters.

Studies on histopathology

Rat livers were fixed in a 10% neutral formalin solution, desiccated in rated alcohol & paraffin embedded. Well slices were put on glass slides then counter-stained through Eosin & Hematoxylin used on behalf of light microscopic examination.

Analytical statistics

The data is shown as Mean S.E.M. for each group (n=6). For the difference between the control & management groups, ANOVA with one way was utilized, followed by Tukey post hoc analysis.

Results

Studies of acute toxicity

The aqueous extract of *Pongamia Pinnata* Linn. leaves remained set up to be not dangerous, as not at all animals died after being given a dosage of 2000mg/kg orally & the animals did not exhibit slightly significant behavioural changes.

The effects of biochemical parameters

When compared to the control group, animals given anti TB medicines (toxic control) had significantly higher ($P \leq 0.05$) SGPT, SGOT, ALP, total cholesterol & total bilirubin levels. When associated to toxic control, APP 200mg/kg & 400mg/kg given with 1hr. previous administration of anti-TB medicines indicated an important decrease in serum diagnostic liver enzymes. Table 1 shows the outcomes.

Table 1
Result of aqueous extract of *Pongamia Pinnata* Linn. leaves on serum biochemical values

GROUP S	TREATMENT	SGOT (iu/l)	SGPT (iu/l)	ALP (iu/l)	TOTAL BILIRUBIN (iu/l)	Total Cholesterol (Mg./dl.)
GROUP - 1	Control	128.76±7.32	65±4.12	188±6.78	0.12±0.02	86.6±6.6
GROUP - 2	Anti TB drugs (Toxic control)	390.50±18.70 #	645.45±18.12 #	324.45±8.76 #	0.41±0.03 #	136.3±18.4
GROUP - 3	Silymarin (100mg/Kg)	168.78±3.92 ^{^^}	138.24±6.23 [^]	142±7.23 ^{^^^}	0.06±0.04 ^{^^}	89.6±5.6 ^{^^}
GROUP - 4	APP (200mg/Kg)	312.76±9.12 [^]	294±14.24 [^]	211.45±7.23 ^{^^}	0.17±0.03 [^]	131.2±14.7 ^{^^}
GROUP - 5	APP (400mg/Kg)	211.67±13.80 ^{^^}	196.45±17.23 ^{^^}	163.23±6.23 [^]	0.12±0.07 ^{^^}	121.2±12.2 ^{^^}

Statistics are stated as Mean±S.E.M (n=6), 1-way ANOVA Tukey post hoc; #p≤0.05 vs. Control (Group - 1); [^]p≤0.05 vs. Toxic Control (Group - 2); ^{^^}p≤0.01 vs. Toxic Control (Group - 2); ^{^^^}p≤0.001 vs. Toxic Control (Group - 2).

Anti-oxidant characteristics in vivo

Anti-oxidant factors were measured in the liver homogenate in this investigation. When paralleled to the control group, oral direction of anti TB medicines (Toxic

Control) considerably ($P \leq 0.05$) lowered SOD, GSH, GRx, GPx, CAT & considerably ($P \leq 0.05$) enhanced TBARS. After associated towards toxic control, APP 200mg/kg & 400mg/kg per 1 hr. former treatment of anti-TB medicines considerably enhanced enzymatic & non-enzymatic levels and dramatically reduced TBARS points. Table – 2 summarizes the findings.

Table 2
Result of aqueous extract of Pongamia Pinnata Linn. leaves on anti-oxidant values in rats

Group	Treatment	SOD ($\mu\text{mol.}/\text{min.}/\text{mg.}$)	Catalase ($\mu\text{mol.}/\text{min.}/\text{m g.}$)	Gpx ($\mu\text{mol}/\text{min}/\text{mg.}$)	Grx ($\mu\text{mol}/\text{min}/\text{mg.}$)	TABRS ($\text{nm}/\text{min}/\text{mg.}$)	GSH ($\text{nm}/\text{min}/\text{mg.}$)
Group 1	- Control	4.62 \pm 0.34	36.12 \pm 0.32	29.32 \pm 0.32	32.12 \pm 0.12	36.12 \pm 1.32	3.12 \pm 0.32
Group 2	- Anti - TB medicines (Toxic control)	2.82 \pm 0.31#	16.32 \pm .78#	13.23 \pm 0.64#	19.12 \pm 0.42#	90.23 \pm 6.72#	0.79 \pm 0.02#
Group 3	- Silymarin (100mg/Kg)	4.12 \pm 0.23 [^]	34.12 \pm 0.12 ^{^^}	31.12 \pm 0.12 ^{^^}	32.12 \pm 0.66 ^{^^^}	34.12 \pm 3.46 ^{^^}	3.12 \pm 0.02 [^]
Group 4	- APP (20mg/Kg)	3.12 \pm 0.13 [^]	24.67 \pm 0.76 [^]	21.12 \pm 0.32 [^]	23.12 \pm 0.12 [^]	48.12 \pm 4.32 [^]	1.23 \pm 0.06 [^]
Group 5	- APP (400mg/Kg)	3.45 \pm 0.46 [^]	31.23 \pm 0.67 ^{^^}	26.78 \pm 0.78 [^]	28.56 \pm 0.12 ^{^^}	36.12 \pm 2.78 [^]	1.92 \pm 0.12 [^]

Statistics are stated as Mean \pm S.E.M (n=6), 1-way ANOVA Tukey post hoc; # $p \leq 0.05$ vs. Control (Group - 1); [^] $p \leq 0.05$ vs. Toxic Control (Group - 2); ^{^^} $p \leq 0.01$ vs. Toxic Control (Group - 2); ^{^^^} $p \leq 0.001$ vs. Toxic Control (Group - 2).

Histological study of the liver

When associated to normal control group animals, histopathological analysis of the liver revealed considerable necrosis of liver cells and inflammation in the centrilobular area, as well as portal triaditis. Hepatocellular necrosis was protected by APP 400mg/kg, and the lobular organisation of the animals was normal (figure 1 to 5).

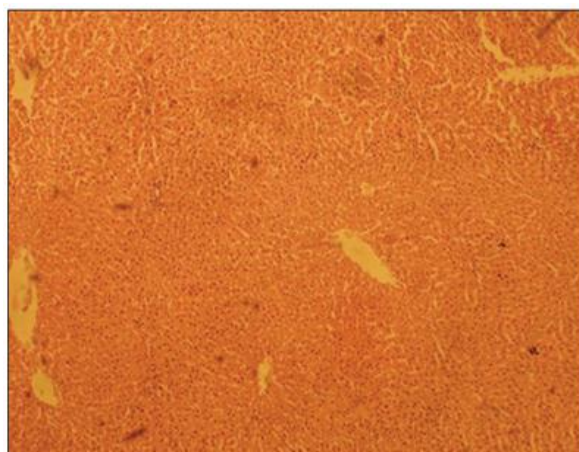


Figure 1. Control

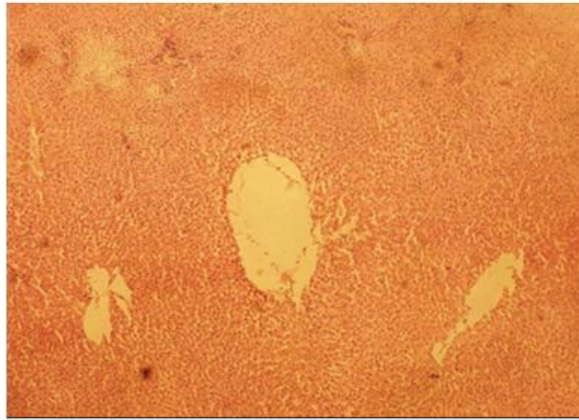


Figure 2. Toxic control

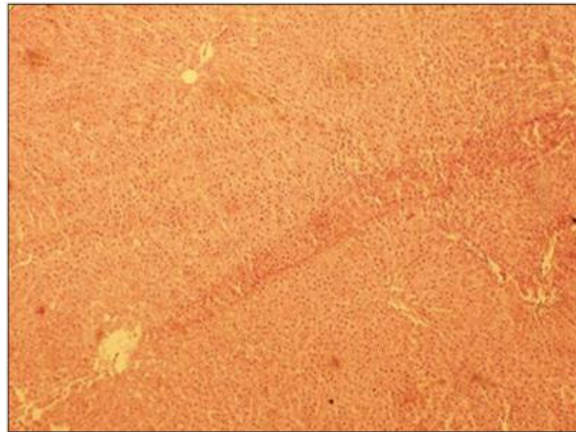


Figure 3. Silymarin (100mg/kg) + ATM

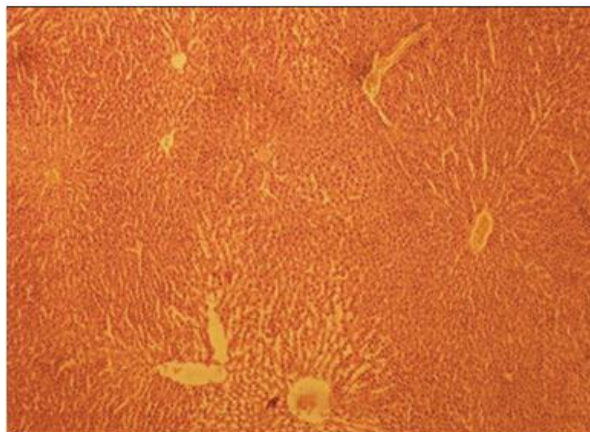


Figure 4. APP (200Mg/kg) + ATM



Figure 5. APP (400mg/kg) + ATM

Discussion

Anti-tubercular medication hepatotoxicity is a serious adverse drug reaction that results in a high rate of morbidity & mortality. Isoniazid, rifampin & pyrazinamide are all possibly hepatotoxic drugs, but their toxicity is amplified when used together [25]. A mixture of anti-TB medicines was employed to cause hepatotoxicity in experimental mice in the current investigation [26]. Hepatic injury was validated by raised points of serum investigative enzymes like SGOT, SGPT & ALP points, as displayed in table -1. Everyday supervision of anti-TB medicines (HR) for 21 days resulted in hepatic damage, as shown in table -1. Due to liver tissue destruction, these enzymes trickle out of the liver and into the blood stream during hepatic injury. The points of these liver marker enzymes in serum remained near common after APP treatment, which could be due to plasma membrane stabilization besides restoration of hepatic tissue destruction produced through anti-TB medications. Cirrhotic liver disease effects hepatotoxicity, which leads to an increase in bilirubin release [27]. The fact that APP therapy reduced bilirubin levels to near normal levels could be related to its inhibitory action on mitochondrial enzymes involved in the metabolism of anti-TB medicines.

Cholesterol points are higher, which could be attributable to tissue acceptance of LDL from the blood [28]. SOD, CAT & GPx are a group of anti-oxidant enzymes that work together to form a defensive system against reactive oxygen species (ROS) [29]. Due to an increased generation of superoxide anions, SOD activity in toxic control mice reduced dramatically in this study. In liver control mice, the activity of H₂O₂ scavenging enzymes CAT and GPx fell considerably. Extreme superoxide anions can deactivate SOD, resultant in an activation of H₂O₂ scavenging enzymes, resulting in a reduction in these enzyme activity. The APP therapy successfully stopped the decline in SOD, CAT, and GPx activity.

Anti -TB medications cause cellular harm by inducing oxidative stress, which is produced by the hepatic antioxidant defence system failing. The prooxidant-anti oxidant balance deteriorates as antioxidant defences are depleted and/or free radical generation rises, resulting in oxidative stress-induced cell loss. Improved

lipid peroxidation was suggested by a significant rise in the application of TBARS in toxic control animals [30]. *Pongamia Pinnata* treatment lowered hepatic lipid peroxidation and prevented anti-TB medication induced rise of TBARS levels, implying that *Pongamia Pinnata* inhibited hepatic lipid peroxidation. It suggests a decline in free radical production & as a result, a reduction in hepatocellular membrane damage.

GSH is transformed to glutathione disulfide and depleted during oxidative stress, resulting in lipid peroxidation. As a result, GSH serves as a marker for assessing oxidative stress. The observed decrease of in toxic control animals could be attributable to increased usage. Hepatic GSH content was recovered after APP therapy. The action of APP could be attributable to a decrease in hepatic peroxidative activity, which leads to a restoration of GSH levels. APP has been shown to diminish hazy edoema, fatty degeneration, severe bleeding, and hepatocellular necrosis in histological studies. The anti-TB medication induced histological alterations were corrected after treatment with APP, suggesting that APP's hepatoprotective efficacy against anti-TB medication prompted hepatotoxicity may be attributed to its ability to reduce oxidative stress.

Conclusion

According to the findings, APP displays hepatoprotective action at a dosage of 400mg/kg when related to a toxic control. Phytochemical analysis of APP indicated the occurrence of carbohydrates, steroids, glabrin, tannins, flavonoids, phenolic compounds, dimethoxy-kanugin, reducing sugars, alkaloids, glycosides & fixed oils all of which contribute to antioxidant capacity & most likely, are responsible for hepatoprotective effects.

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