PROTECTIVE EFFECT OF ANDROPRAPHIS PANICULATA AQUEOUS EXTRACT (EAAp) AGAINST ISONIAZID AND RIFAMPICIN-INDUCED RAT LIVER DAMAGE

Risdawati Djohan¹, Ambar Harjanti², Pendrianto³
¹Risdawati Djohan, Department of Pharmacology, Faculty of Medicine, and Biomedical Science, Universitas Yarsi, Jakarta
²Ambar Harjanti, Department of Parasitology, Faculty of Medicine, Universitas Yarsi, Jakarta
³Pendrianto, Integrated Research Institute, Universitas Yarsi, Jakarta
Email: risdawati@yarsi.ac.id, ambar.harjanti@yarsi.ac.id, pendrianto@yarsi.ac.id
Corresponding Author: risdawati@yarsi.ac.id

ABSTRACT

Isoniazid (INH) and rifampicin (RIF) are first-line antituberculosis drugs (OAT) in tuberculosis treatment that are used for at least 6 months. The use of OAT has been associated with toxic reactions in the liver and causes hepatitis. This study aimed to determine the effect of an aqueous extract of Andrographis paniculata (EAAp) on liver damage induced by INH and RIF. Method: Male Sprague-Dawley rats weighing 250–300g were divided into 5 groups, each consisting of 6 mice. Animals were given isoniazid and rifampicin at 100 mg/kg, respectively, to induce liver damage, silymarin (25 mg/kg) for the positive control group, and Ap extract at doses of 200mg and 300 mg/kg for the test group. All treatments were given orally once daily for 28 days. Measurement of serum aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin, and liver histopathology levels was carried out to determine the effect of EAAp on liver damage by INH and RIF. Results: Rats treated with INH+RIF were hepatotoxic, as evidenced by increased serum ALT, AST, and ALP activity, total bilirubin levels, and histopathological changes in the liver. Administration of Ap extract doses of 200 mg/kg and 300 mg/kg significantly decreased liver biochemical and histological changes caused by OAT. Conclusions: EAAp has a protective effect against hepatotoxic-induced INH and RIF in animal models.

INTRODUCTION

Tuberculosis is still a major public health problem worldwide. About a third of the world’s population has the disease, which claims nearly three million lives each year (Gill et al., 2020). Isoniazid (INH) and Rifampicin (RIF) are first-line drugs for the treatment of tuberculosis used in the form of combination therapy for at least 6 months (Indonesia, 2020). Single-use of isoniazid and rifampicin or in combination form can cause liver damage and result in liver failure of approximately 5%–22% in cases of acute liver failure (Zhuang et al., 2022). The pathogenesis of liver damage by INH is not yet fully understood. Some reports suggest that protoporphyrin IX accumulation, oxidative stress, mitochondrial damage, drug metabolism enzymes, endoplasmic reticulum stress, bile transport imbalance, and immunological response are the main mechanisms of liver damage by INH (Zhuang et al., 2022).
Hepatotoxicity by INH and RIF is also associated with the role of toxic intermediate compounds (metabolites) and reactive oxygen species (ROS) produced in INH metabolism. Enzymes in the liver, N-acetyltransferase and amidohydrolase, metabolize INH directly or indirectly into the toxic metabolites acetylhydrazine and hydrazine. Acetylhydrazine produces reactive acetylated species that can bind to hepatic proteins covalently. In addition, oxidative stress by reactive oxygen species (ROS) mediated by cytochrome P450 2E1 (CYP2E1) also has a role in hepatotoxicity caused by hydrazine. RIF, a potent inducer of CYP2E1, may worsen liver damage by INH by increasing the production of toxic metabolites such as hydrazine (Xin Liu et al., 2017).

Liver protection against damage caused by toxic substances can be done by reducing oxidative stress, inhibiting the inflammatory process, and preventing apoptosis (Rahmani et al., 2023). Oxidative stress induces the expression of pro-inflammatory cytokines such as TNF-α, which facilitates the occurrence of an inflammatory response that will cause liver damage. TNF-α also plays a role in inducing the extrinsic pathway of apoptosis by binding to death receptors and activating caspase-3 (Fouad et al., 2019). Another study (Bhilare et al., 2020) showed that the use of the antioxidant bile acid (ursodeoxycholic acid) incorporated in INH succeeded in reducing oxidative stress and maintaining normal levels of the enzymes glutathione peroxidase and superoxide dismutase so that liver function returned to normal. Activity-hepatoprotective natural products such as polyphenols, terpenoids, and alkaloids can increase the expression of Nrf2, which is an important protein in the hepatocyte antioxidant defense system (Iranshahy et al., 2018).

The use of conventional and synthetic drugs to treat liver disease does not seem to be satisfactory and can also cause adverse effects, so treatment is now shifting to complementary and alternative healing (Bardi et al., 2014). The hepatoprotective effects of several medicinal plants that have been tested can provide better benefits if used together with conventional drug treatment to prevent liver damage by various chemical toxins and drugs. This is because medicinal plants contain compounds that have antioxidant activity, so they can reduce liver damage by reducing oxidative stress.

Some medicinal plants, including Vitex negundo, Boesenbergia rotunda, Phyllanthus niruri, Ipomoea aquatic, Orthosiphon stamineus, Zingiber officinalis, Caesalpinia sappan, and Andrographis paniculata (Bardi et al., 2014), as well as several others (Ugwu & Suru, 2021), have hepatoprotective activity. Andrographis paniculata is reported to have hepatoprotective activity induced by CC14, d-galactosamine, concanavalin A, tetracycline, acethaminophen, and alcohol (Xin Liu et al., 2017), tert-butylhydroperoxide (t-BHP) (Chao & Lin, 2012), thioacetamide (Bardi et al., 2014), and metotreksat (Parhasarathy & Prince, 2023). However, there has been no evidence to suggest that A. paniculata is also effective for protecting against liver damage induced by INH and RIF.

The mechanism of liver protection by toxic substances is developed, among others, through eliminating reactive oxygen species (ROS), controlling cytokine secretion, and preventing apoptosis caused by immunological disorders (Bardi et al., 2014) (Parhasarathy & Prince, 2023). This study aimed to evaluate the possible hepatoprotective effects of A. paniculata leaf extract in vivo in an INH+Rif-induced rat by measuring liver function biomarkers, histological changes, body weight, liver weight, and liver index of the rat. The results were compared with the effects of silymarin, a drug that has been used as a hepatoprotector.

**METHOD**

**Material**

Simplisia Andrographis paniculata (herb sambiloto) obtained from Dra. Mauizzati Purba, Apt, M. Kes, Director of the Directorate of Original Indonesian Medicine of the Food and Drug Control Agency (BPOM), Kit for measurement of AST, ALT, and ALP, total bilirubin and direct bilirubin obtained from Glory, sodium carboxymethyl cellulose (Na CMC) and Rifampicin purchased from pharmacies, Silymarin and isoniazid purchased from Sigma-Aldrich.
Experimental animals
Healthy adult male Sprague Dawley (SD) rats, aged 2-3 months, weighing 150–200 g, were obtained from the Non-Ruminant and Satwa Harapan Laboratory, Department of Animal Production Science and Technology, Bogor Agricultural University (IPB). This research was approved by the Research Ethics Committee of the Research Institute of YARSI University, Indonesia (No. 075/KEP-UY/BIA/III/2017). All experimental animals received treatment in accordance with the Guide for the Care and Use of Laboratory Animals (Research., 2010). Rats are placed in cages in animal rooms at room temperature, with a humidity of 50–60% and a light/dark cycle of 12 hours. Animals are kept on a standard pellet diet and ad libitum drinking water. All animals were acclimatized to standard laboratory conditions for 7 days prior to the experiment.

Experimental design
The rats were randomly divided into five groups: the control group (healthy control), the INH-RIF group (inductor), the silymarin group (positive control group), the EAAp200 group, and the EAAp300 group (treatment group), each consisting of six mice (Table 1). Silymarin and EAAp are given 30 minutes before administration of isoniazid and rifampicin. All experiments were given orally, once daily for 28 days (Sanjay et al., 2021).

Weighing rats is carried out every 3 days. At the end of the experiment, 24 hours after the last treatment, the mice were sedated with ketamine (30 mg/kg, 100 mg/mL) and xylazin (3 mg/kg, 100 mg/mL) (Bardi et al., 2014). Blood is drawn through the heart and collected in a vacutary tube. The blood sample was centrifuged for 15 minutes at 2500 rpm to obtain serum. Serum is stored at -20 degrees Celsius to determine serum levels of AST, ALT, ALP, total bilirubin, and direct bilirubin. The abdominal cavity and chest of the rat were opened, and the liver was taken and then washed with cold saline, then placed on filter paper and weighed. Liver specimens are fixed in a 10% neutral buffer formalin (NBF) solution for histopathology examination.

Table 1. Treatment groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>CMC 0.5% (vehicle)</td>
</tr>
<tr>
<td>INH+RIF</td>
<td>Isoniazid (100mg/kgBW) + Rifampin (100mg/kgBW)</td>
</tr>
<tr>
<td>Silymarin</td>
<td>Silymarin (25mg/kgBW) + Isoniazid (100mg/kgBW) + Rifampin (100mg/kgBW)</td>
</tr>
<tr>
<td>EAAp200</td>
<td>EAAp (200mg/kgBW) + Isoniazid (100mg/kgBW) + Rifampin (100mg/kgBW)</td>
</tr>
<tr>
<td>EAAp300</td>
<td>EAAp (300mg/kgBW) + Isoniazid (100mg/kgBW) + Rifampin (100mg/kgBW)</td>
</tr>
</tbody>
</table>

Calculation of the number of samples
The number of samples is calculated using the following formula (Rasool et al., 2010):

\[ n > \frac{2\{((Z_\alpha + Z_\beta) s) / \delta\}^2}{\delta} \]

where
- \( n \) = number of samples
- \( Z_\alpha = 1.96, Z_\beta = 1.28 \) for 90% power and significance level \( p < 0.05 \).
- \( s \) = standard deviation (SD)
- \( \delta \) = minimum effect difference, set at 30% for SD 15%.

After calculating with the formula above, the number of samples in this study is 6 groups.

Preparation of A. paniculata water extract (EAAp)
Dried A. paniculata samples are sorted and then mashed into powder. Approximately 50 grams of powder are mixed into 500 mL of water, soaked for 6 hours with regular stirring, and then left (without stirring) for about 12 hours. The filtrate obtained is concentrated using a rotary evaporator and dried...
using a freeze-dryer (Rafi et al., 2020). Furthermore, an analysis of EAAp was carried out to determine the levels of active compounds and their contamination. The extract was stored in sealed brown bottles at 4°C for further analysis.

**Preparation of a 0.5% Na-CMC suspension**
A total of 0.5 g Na-CMC is added to 10 mL of hot aqua dest and then left for about 15 minutes to obtain a clear and homogeneous mixture, then diluted with aqua dest to 100 mL. This suspension is used as a carrier/vehikel for EAAp, silymarin, INH, and Rifampicin.

**Preparation of INH, Rifampicin, Silymarin, and EAAp suspensions**
Two hundred milligrams of INH are suspended in a mortar by adding 0.5% Na-CMC suspension little by little while stirring until a homogeneous mixture is obtained, then adding 0.5% Na-CMC suspension to 10 ml. The same procedure is performed to make suspensions of rifampicin (200mg), silymarin (50 mg), and EAAp (400 and 600 mg).

**Measurement of serum levels of ALT, AST, ALP, total bilirubin, and bilirubin in rat serum**
The levels of ALT, AST, ALP, total bilirubin, and bilirubin in rat serum were spectrophotometrically measured according to the procedure in the manual kit used.

**Statistical analysis**
The results of the study are presented as the average value of ± SE. Data were analyzed using SPSS for Windows software version 24, with a one-way analysis of variance (ANOVA) test followed by a post hoc LSD test. For data that does not meet the parametic test requirements, the Kruskal-Wallis test is used. The statistical significance is set at 0.05.

**RESULTS AND DISCUSSION**

**Characteristics of Andrographis paniculata Water Extract (EAAp)**
The extraction results of Andrographis paniculata leaves in the form of a thick blackish-green extract do not contain microbes or active compound levels, as andrographolide 0.62 mg/mL was analyzed by high-performance liquid chromatography (HPLC). The full results of the EAAp analysis are presented in Table 2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water content</td>
<td>5.15 %</td>
</tr>
<tr>
<td>Ash content</td>
<td>31.38 %</td>
</tr>
<tr>
<td>Acid insoluble ash content</td>
<td>0.88 %</td>
</tr>
<tr>
<td>Water soluble juice content</td>
<td>66.06 %</td>
</tr>
<tr>
<td>Soluble ethanol juice content</td>
<td>23.27 %</td>
</tr>
<tr>
<td>Microbe</td>
<td></td>
</tr>
<tr>
<td>TPC (Total plate count)</td>
<td>negative</td>
</tr>
<tr>
<td>Colliform</td>
<td>negative</td>
</tr>
<tr>
<td>Mold/Kamir</td>
<td>negative</td>
</tr>
<tr>
<td>Heavy Metals</td>
<td></td>
</tr>
<tr>
<td>Pb</td>
<td>5.48 ppm</td>
</tr>
<tr>
<td>Cd</td>
<td>1.28 ppm</td>
</tr>
<tr>
<td>As</td>
<td>*</td>
</tr>
<tr>
<td>Andrografolide</td>
<td>0.62 mg/mL</td>
</tr>
<tr>
<td>*Undetectable</td>
<td></td>
</tr>
</tbody>
</table>
The effect of EAAp on body weight, weight, and rat liver index was induced by INH+RIF.

The rats' body weight was weighed every 3 days to determine the change in body weight during the experiment. Almost all experimental animals experienced weight loss until day 3, except for the EAAp300 group, where weight loss occurred until day 6 (Figure 1). Compared to the other groups, rats with liver damage caused by INH+RIF showed the least increase in body weight (2.4%) compared to the control group (11.7%), silymarin (11.1%), EAAp200, and EAAp300 by 7% and 4.3%, respectively. However, the liver weights of rats with liver damage by INH+RIF were heavier, and the liver index was higher than the other groups (Table 2). Giving EAAp 30 minutes before INH + RIF induction can reduce rat liver weight and liver index markedly, namely by 3.06 ± 0.12% (p<0.001), while in the EAAp200 and 3.16 groups ± 0.12% in the EAAp300 group (p<0.001), and the value is no different from the silymarin group.

![Figure 1. Changes in rat body weight for 28 days](image)

Table 3. Effect of EAAp on body weight, liver weight, and liver index (n = 6)

<table>
<thead>
<tr>
<th>Groups</th>
<th>Body Weight (BW) (g)</th>
<th>Liver Weight (LW) (g)</th>
<th>Liver Index (LW/BW) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (CMC 0.5%)</td>
<td>178 ± 8.90</td>
<td>6.09 ± 0.66</td>
<td>3.42 ± 0.10</td>
</tr>
<tr>
<td>INH+RIF (@100 mg/kg BW)</td>
<td>158 ± 4.10</td>
<td>6.97 ± 6.66</td>
<td>4.41 ± 0.17*</td>
</tr>
<tr>
<td>Silymarin (25 mg/kg BW) + (INH+RIF)</td>
<td>176 ± 9.10</td>
<td>5.89 ± 5.57</td>
<td>3.35 ± 0.17**</td>
</tr>
<tr>
<td>EAAp200 (200 mg/kg BW) + (INH+RIF)</td>
<td>167 ± 6.10</td>
<td>5.18 ± 5.25</td>
<td>3.10 ± 0.11***</td>
</tr>
<tr>
<td>EAAp300 (300 mg/kg BW) + (INH+RIF)</td>
<td>161 ± 5.10</td>
<td>5.29 ± 5.48</td>
<td>3.28 ± 0.11***</td>
</tr>
</tbody>
</table>

Data is displayed as the average value of ± SE.
* p<0.05, ** p<0.01 compared to toxin group (INH+RIF)
* p<0.05, compared to controls

Liver index = \frac{\text{Rat liver weight (g)}}{\text{Rat Body weight (g)}} \times 100%

Effect of EAAp on Rat Liver Damage Induced by INH+RIF

Liver damage due to OAT (INH+RIF) was demonstrated by increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and direct and total bilirubin compared to 77% (p < 0.01); 81% (p < 0.001); 199% (p < 0.000); 1289% (p < 0.01); and 487% (p < 0.001) (Figure 2). Serum levels of liver function markers were then verified with pathological changes in the liver. Rats in the INH+RIF treatment group showed histological changes...
characterized by necrosis and vacuolization as well as sinusoid dilatation (Figure 3 and Table 3). EAAP (200 and 300 mg/kg) was able to significantly reduce the increase in serum levels of ALT, AST, ALP, direct bilirubin, and total bilirubin. However, EAAP200 was not effective enough to reduce elevated serum AST levels ($p > 0.05$).

![Image of Figure 2](image-url)

**Figure 2.** Effect of EAAP on serum increases of ALT (A), AST (B), ALP (C), direct bilirubin (D), and total bilirubin (E) in INH+RIF-induced rats (100 mg/kg each). EAAP (200, 300 mg/kg) and silymarin (25 mg/kg) were administered orally to rats for 28 days. The data is displayed as the average value of ± SE (n = 6). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. the INH+RIF group; #$p < 0.01$, $#p < 0.001$ vs. the control group

<table>
<thead>
<tr>
<th>Group</th>
<th>Bile duct cell proliferation</th>
<th>Sinusoid dilatation</th>
<th>Necrosis and vacuolization of epithelial cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (CMC 0.5%)</td>
<td>0/4</td>
<td>0/4</td>
<td>0/4</td>
</tr>
<tr>
<td>INH+RIF</td>
<td>0/4</td>
<td>1/4</td>
<td>2/4</td>
</tr>
<tr>
<td>Silymarin+ INH+RIF</td>
<td>1/4</td>
<td>0/4</td>
<td>0/4</td>
</tr>
<tr>
<td>EAAP200+ INH+RIF</td>
<td>1/4</td>
<td>0/4</td>
<td>0/4</td>
</tr>
<tr>
<td>EAAP300+ INH+RIF</td>
<td>2/4</td>
<td>0/4</td>
<td>0/4</td>
</tr>
</tbody>
</table>
Figure 3. Effect of EAAp on INH+RIF-induced rat liver histology changes. (A) Control rats showed normal hepatocytes around the unaffected portal area; (B) rats induced with INH+RIF showed connective necrosis infiltrated by immune cells (B1, necrosis and vacuolization; B2, sinusoid dilatation); (C) rats were given silymarin (25 mg/kg BW); (D) and (E) rats were given EAAp (200mg and 300 mg/kg BW). The last three groups underwent bile duct cell proliferation. Hematoxylin and eosin staining; 200x magnification Arrows indicate abnormalities occurring.

Studi in Silico
The results of the analysis of the predicted potential of 46 compounds and metabolites obtained from the Kanaya KnapSack database using Way2Drug Pass Server show that the compounds and metabolites of Andrographis paniculata have the potential to protect the liver from damage caused by hepatotoxic substances. There are 9 categories of biological activity related to hepatoprotective, such as membrane integrity agonists (22 compounds), hepatoprotectants (27 compounds), membrane permeability inhibitors (17 compounds), lipid peroxidation inhibitors (14 compounds), free radical scavengers (16), hepatic disorder treatments (16 compounds), antioxidants (12 compounds), anti-inflammatory agents (25 compounds), and immunosuppressants (13 compounds) (Figures 3 and 4a).
Figure 4. Heatmap of biological activity prediction of Andrographis paniculata using the Way2Drug Pass Server. The yellow color indicates a high Pa score visualization.
Liver damage due to the use of isoniazid (INH) and rifampicin is a major trigger of morbidity and mortality in many countries around the world (Su et al., 2021). INH and rifampicin can cause liver injury from mild to severe, ranging from an asymptomatic increase in serum transaminases to severe, such as acute liver dysfunction. In addition, these unexpected effects can also have an impact on decreasing adherence to taking drugs, thereby increasing treatment failure and causing the death of tuberculosis (TB) sufferers, especially in densely populated countries (Sanjay et al., 2021). Currently, tuberculosis...
treatment combined with hepatoprotection is still limited. Our research studied the prophylactic use of an aqueous extract of Andrographis paniculata (EAAp) in animal models (in vivo) with INH and rifampicin-induced liver injury to determine its ability to protect against liver damage.

The weight loss that occurred early in the experiment in almost all of the experimental animals in this study may have been due to reduced food intake due to adapting to the treatment using sonde. This situation was also seen in the control group, which also experienced weight loss until the third day. Animal weight loss at the beginning of the experiment has been widely discussed before, including food shortages arising from changes in feeding habits, activity, and environmental disturbances (Dietze et al., 2016). Compared to other groups, rats in the EAAp300 group showed longer weight loss, which was thought to be due to the bitter taste of EAAp at a dose of 300 mg/kg BW.

We found considerable weight loss in the INH+RIF group compared to the control (11%), while in the EAAp-treated group (200 mg/kg and 300 mg/kg), the weight loss was very small. Similarly, with the liver index, the highest values were seen in the INH + RIF group, and EAAp (200 mg/kgBW and 300 mg/kgBW) was able to return these values close to normal values. This state is thought to be due to reduced inflammation. This state is thought to be due to reduced inflammation by terpenoid compounds such as andrographolide contained in EAAp, which has antioxidant and anti-inflammatory activity (Mussard et al., 2020).

EAAp decreased serum levels of liver biomarkers increased by INH+RIF, improved liver histology, reduced necrotic damage and immune cell infiltration, and reduced elevated liver indexes due to INH+RIF treatment (Table 2, Figure 1). Similar results were also reported by (Bardi et al., 2014) and (Sabina et al., 2019). Andrographis paniculata extract at a dose of 500 mg/kgBW can reduce liver damage caused by thioacetamide in rats by decreasing levels of liver function biomarkers, liver index, and liver histology.

Administration of INH+RIF once daily for 28 days in test rats increased serum levels of ALT, AST, ALP, and bilirubin (direct and total). Serum transaminases are the main enzymes that are passively released into the blood due to damage to hepatocyte cell membranes (Bardi et al., 2014; Sanjay et al., 2021; Kosasih et al., 2019; Sabina et al., 2019; Xiangyan Liu et al., 2020). An increase in bilirubin levels indicates disruption of liver metabolic activity, including due to drug toxicity. Liver damage or injury by the main OAT, namely isoniazid (INH) and its metabolites, occurs during metabolic processes in the liver, thus disrupting mitochondria, endoplasmic reticulum, and plasma membranes. While rifampicin increases INH metabolism by stimulating the liver cytochrome P450 enzyme through its action on hepatocyte-PXR receptors as well as CAR, thereby increasing liver damage (Sanjay et al., 2021).

Histopathological analysis of rat livers given INH+RIF showed liver damage in the form of necrosis and infiltration of immune cells, causing portal expansion with dilation and sinusoid congestion. Histological features of the livers of the silymarin and EAAp groups showed no necrosis (Figure 2). Our study results are similar to previous reports that andrographolide (the main active compound of Andrographis paniculata) was able to protect against paracetamol-induced liver necrosis as well as reduce serum increases in ALT, AST, ALP, and total bilirubin in rats (Basu et al., 2020).

Liver toxicity by isoniazid and rifampicin has been reported due to oxidative stress events caused by toxic metabolites and free radicals, or ROS, produced at the time of drug metabolism in the liver. This is seen in patients who take OAT along with antioxidants to reduce the incidence of oxidative stress and protect against liver damage (Agarwal et al., 2010). In our study, liver damage by INH+RIF was reduced by EAAp at 200 or 300 mg/kg BW, which is thought to be due to the hepatoprotective and antioxidative activity of EAAp (Figures 3 and 4). Sanjay (Sanjay et al., 2021) reported that there is a significant association between the reduction of oxidative stress due to toxic metabolites and free radicals from OAT and the role of nuclear factor erythroid-related factor 2 (Nrf2). Nrf2 is one of the antioxidant transcription factors and increases the expression of GSH and other endogenous
antioxidants under stressful conditions. Some of the genes regulated by Nrf2 are gamma-glutamylcysteine (γ-GCS) genes, glutamate cysteine ligase (GCL), glutathione reductase (GR), glucose-6-phosphate dehydrogenase (G6PDH), GST, and GPx, NAD(P)H dehydrogenase [quinone] 1 (NQO1), HO-1, SOD, CAT, and thioredoxin reductase (TRXR) genes (Mussard et al., 2019).

Khole (Khole et al., 2019) It is also reported that andrographolide plays an important role in the process of altering antioxidant defenses in diseases triggered by oxidative stress by modulating TP53 (Tumor Protein P53) and HNF4A (Hepatocyte Nuclear Factor 4 alpha), in determining miRNAs that will increase regulation of the HO-1 system, glutathione, and thioredoxin. It was also reported that andrographolide can reduce liver pathological changes and oxidative stress in ethanol-fed rats by reducing the expression of NF-kB and TNF-alpha (Song et al., 2020). Some mechanisms of liver protection by toxic substances are developed, among others, through eliminating reactive oxygen species (ROS), controlling cytokine secretion, and preventing apoptosis caused by immunological disorders (Bardi et al., 2014; Parthasarathy & Prince, 2023).

Analysis of the biological activity of Andrographis paniculata with Way2Drug PassServer shows that there are about 9 categories of activity that are predicted to have a role related to hepatoprotectiveness. Cellular homeostasis is highly dependent on the integrity of the plasma membrane. Damage to plasma membranes due to stress in the intra- and extracellular environment can arise due to the use of drugs. The cells have the ability to restore membrane integrity through repair pathways (Ammendolia et al., 2021) and the role of potential compounds as membrane integrity agonists and membrane permeability inhibitors (Martel et al., 2012). So that fatal impacts such as cell death can be avoided. The activity of lipid peroxidation inhibitors in a compound can play a role in reducing cell damage. It is known that lipid peroxidation triggers damage to cell membranes and mitochondria, resulting in impaired mitochondrial function, which is the underlying cause of cell death (Fedotcheva et al., 2023). The Pa values of the six categories of hepatoprotective-related biological activity of the compounds contained in Andrographis paniculata are not much different from the Pa values of silymarin (Figure 5), which have been proven to be hepatoprotectants. This proves that the hepatoprotective activity of EAAP can also be relied on.

CONCLUSION

This study shows that the use of an aqueous extract of Andrographis paniculata (EAAp) can be an effective strategy to prevent liver cell damage due to the use of isoniazid and rifampicin (INH and RIF). EAAp at doses of 200 mg/kg and 300mg /kg was able to reduce the increase in serum levels of liver biomarkers to a decreased liver index due to improvements in body and liver weight. From the histological picture of the liver, EAAp also played a significant role in suppressing damage. EAAp’s hepatoprotective effects are thought to relate to its ability to reduce oxidative stress, be anti-inflammatory, etc.

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Protective Effect of Andropraphis Paniculata Aqueous Extract (Eaap) Against Isoniazid and Rifampicin-Induced Rat Liver Damage


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