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Evaluation of the Hepatoprotective Activity of *Curcuma xanthorrhiza*, *Garcinia mangostana* Rind, *Scurrula atropurpurea*, and their Combination based on Biochemical and Histopathological Parameters

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Abstract

Background: Hepatotoxicity is a major side effect of Fixed Dose Combination (FDC-ATD) antituberculosis drugs that can hinder the success of therapy. *Curcuma xanthorrhiza* (CXE), *Garcinia mangostana* peel (MRE), and Tea Mistletoe (TME) extracts rich in flavonoids and polyphenols have been reported to have antioxidant and anti-inflammatory activities, but comparison of the hepatoprotective effects between single extracts and their combinations is still limited. **Aim:** This study aimed to evaluate and compare the hepatoprotective effects of CXE, MRE, TME, and their combination on FDC-ATD-induced liver damage. **Methods:** A pre-post test experimental study with a control group involved 25 male Wistar rats divided into five groups, consisting of Hepatotoxic Control (Hepa-C) and four treatment groups (CXE, MRE, TME, and the combination of extracts), with hepatotoxicity induced by administration of FDC-ATD for seven days at an isoniazid-equivalent dose of 300 mg/kg body weight; evaluation was conducted by measuring Serum Glutamic Pyruvic Transaminase (SGPT) levels, Glutathione (GSH) concentrations, and liver histopathology examination. **Results:** Compared to the Hepa-C group, all treatment groups showed a significant decrease in SGPT levels and an increase in GSH levels ($p < 0.05$), accompanied by a decrease in the degree of hepatocellular degeneration and necrosis and better preservation of liver lobule structure in all extract groups ($p < 0.05$); the combination of extracts provided the greatest hepatoprotective effect although not statistically significantly different from the single extracts. **Conclusion:** CXE, MRE, and TME, both individually and in combination, are able to reduce oxidative stress and maintain liver cell integrity, thus having the potential to be developed as a complementary therapy to reduce hepatotoxicity caused by antituberculosis drugs.

Major Findings: The combination and single extracts of CXE, MRE, and TME demonstrated consistent hepatoprotective activity against FDC-ATD-induced hepatotoxicity through decreased SGPT, increased GSH, and improved liver histology.

Keywords: *C. xanthorrhiza*, GSH, Hepatoprotector, Mangosteen Rind, SGPT, Tea Mistletoe,

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1. Introduction

Hepatotoxicity was the condition of liver cell damage that caused by several factors such as Drug-induced Hepatitis (DIH) and Drug-induced Liver Injury (DILI)[1]. Fixed-dose Combination Anti-tuberculosis Drugs (FDC ATDs) are one of DILI classes. According to Global TB Report 2024 by the World Health Organization (WHO), Indonesia has the second-highest rank of TB cases[2,3]. Due to the high TB cases in

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Indonesia has led to widespread use of long-term FDC ATDs and increasing the risk of hepatotoxic events. Globally, FDC ATDs are reported to contribute to 2%-28% of DILI cases[4].

The caused hepatotoxicity by FDC ATDs are overproduction of Reactive Oxygen Species (ROS) in hepatocytes, which results in biochemical and morphological liver damage[1,5,6]. Hepatoprotective agent are needed to prevent or reduce the hepatotoxicity adverse effects of FDC ATDs. Natural products such as *C. xanthorhiza* Extract (CXE), Mangosteen Rind Extract (MRE; *G. mangostana* L.), and Tea Mistletoe Extract (TME; *S. atropurpurea* Dans.) have been reported to antioxidant properties that may confer hepatoprotective effects[7]. These extracts are thought to antioxidant activity by stabilising superoxide radicals, inhibiting inflammatory pathways, and modulating oxidative stress[8,9]. Additionally, their flavonoid, polyphenol, and xanthone constituents, such as α-mangostin and β-mangostin, have shown potential in reducing liver cell damage[10-13].

Hepatoprotective properties from this natural extract can be assessed using specific particular biomarker of liver damage and function. These consist of Serum Glutamic Pyruvic Transaminase (SGPT), Glutathione (GSH), and liver histopathology[14-16]. SGPT are a specific marker of liver cell injury, as it is predominantly found in hepatocytes and leaks into the bloodstream upon cellular damage[17]. GSH are a key endogenous antioxidant, and its depletion reflects increased oxidative stress and impaired detoxification capacity[18-22]. Liver histopathology provides direct visual evidence of hepatocellular damage and the degree of tissue recovery.

Consider of antioxidant properties from CXE, MRE, and TME, it is necessary to evaluate their effectiveness in preventing liver injury induced by FDC ATDs. This study aims to assess the hepatoprotective effects of single and combination extracts by evaluating changes in SGPT levels, GSH concentrations, and histopathological liver improvements, thus providing an evidence-based perspective on their therapeutic potential.

2. Materials and Methods

2.1 Extraction and Phytochemical Screening

Regarding the verification of the plant samples, the UPT-Laboratorium of Setia Budi University, Surakarta, has performed determination tests on the extracted plants, documented under letter numbers 142/DET/UPT-LAB/13.08.2024, 144/DET/UPT-LAB/7.09.2024, and 143/DET/UPT-LAB/13.08.2024. The extract was made by soaking the plants in 96% ethanol (1 part plant to 5 parts ethanol) for 72 hours. The extract was separated from the plant using filter paper. The liquid extract was separated from solvent to produce a concentrated extract using rotary evaporator (40° C) for 1 hour, then the concentrated extract was dried over Synthetic Amorphous Silica (SAS) until the dry extract to plant ratio reached 5:1, with a water content of less than 10 %.

Phytochemical screening tests are performed to verify the presence of flavonoids, polyphenols, and anthraquinones. Flavonoid analysis means checking for a specific part of flavonoids that absorbs UV light at 366 nm, which causes them to fluorescence. The combination of $FeCl_3$ with hydroxyl groups in phenolic compounds attached to unsaturated carbon creates a bluish-black complex, indicating the presence of polyphenolic compounds[8]. Anthraquinone detection involves the addition of H_2SO_4 and ammonia, resulting in a distinctive pink colour caused by Borntrager's reaction between ammonia and anthraquinone[23].

2.2 Experimental Design

Twenty-five male Wistar strain rats, each weighing between 170 and 220 grams and having normal SGPT levels (17.5-30.2 U/L), were used for the hepatoprotective study and split into five groups (5 rats per groups). The method used was a randomised controlled trial with a hepatoprotective effect seen with administration of extract at the same time with isoniazid (300 mg/kg body weight) was introduced. The hepatotoxic doses of INH for rats was based on the lowest published specifically 250-400 mg/kg in rats. One hour post-induction, each group received the following treatment:

Group 1: Hepatotoxic Control (Hepa-C) CMC-Na 0.5%.

Group II: *C. xanthorrhiza* Extract (CXE) 150 mg/kg.

Group III: Mangosteen Rind Extract (MRE) 200 mg/kg.

Group IV: Tea Mistletoe Extract (TME) 250 mg/kg.

Group V: Combination Extract (CE). The composition of CXE, MRE, and TME was compared using a ratio of 3: 4: 5[24-26].

The dosage selection was based on a systematic review of several journals that have conducted research on the hepatoprotective activity of these extracts separately. In this study, a trial was conducted by reducing the doses from the review results to assess the hepatoprotective effect at low doses. The combination dosage used was based on a single dose combination to assess the synergistic hepatoprotective effect of the extract combination. The results of this study require further research to determine the optimal dosage for the hepatoprotective effect of these extracts[1,25,26].

The Hepa-C group proposes a liver hepatotoxic model caused by FDC ATDs, leading to an SGPT level that is more than five times higher than normal[27]. The experimental groups contain the CXE, MRE, and TME categories, in addition to a group that combines all three extracts (CE). The Health Research Ethics Committee of the UMS Faculty of Medicine has approved this investigation based on an ethical feasibility letter with the number 5263/B.1/KEPK-FKUMS/VIII/2024.

2.3 Measurement of Serum Glutamic-pyruvic Transaminase (SGPT) as Biochemical Parameter

SGPT levels were assessed prior to and on the seventh day of treatment using a StarDust MC15 UV Spectrophotometer with a wavelength (λ) of 340 nm and reagents (GPT) FS DiaSys® R1 (Cat No. 1 2701 99 83 021) and R2 (Cat No. 1 2701 99 83 022).

2.4 Histopathology of Liver

The histopathology test sample was a liver organ obtained using the surgical method on the seventh day of treatment. Before testing, the sample was weighed, rinsed with 0.9% NaCl, and stored in a 10% BNF solution. The sample was subsequently cut to 4 µm using a microtome, and Hematoxylin and Eosin (H and E) were used to stain the tissue. The quantitative results of the number of normal cells and the quantity of pyknosis, karyorrhexis, and karyolysis cell damage were used to evaluate the histopathology results. The stained slices were examined with a CKX3 OLYMPUS® Microscope.

2.5 Glutathione Assay

A Biotek Epoch® Elisa Reader with a wavelength of ° 412 nm was used to read the levels of GSH in blood serum samples. GSH assay kit reagent (Abbkine®) with Cat No. KTB1600 was added.

2.6 Data Analysis

Data analysis was support by IBM SPSS Statistics software. The SGPT and GSH data were analysed using the Kruskal-Wallis test, subsequently going through the Mann-Whitney test was significance result of $p< 0.05$. The remaining data were analysed using one-way ANOVA with significance result of $p < 0.05$, followed by a post-hoc Tukey's test to see which group was significant different from the control group.

3. Result

3.1 Moisture Content and Phytochemical Screening

The water content assays conducted on the CXE, MRE, and TME samples yielded results of 5.35%; 3.70%; and

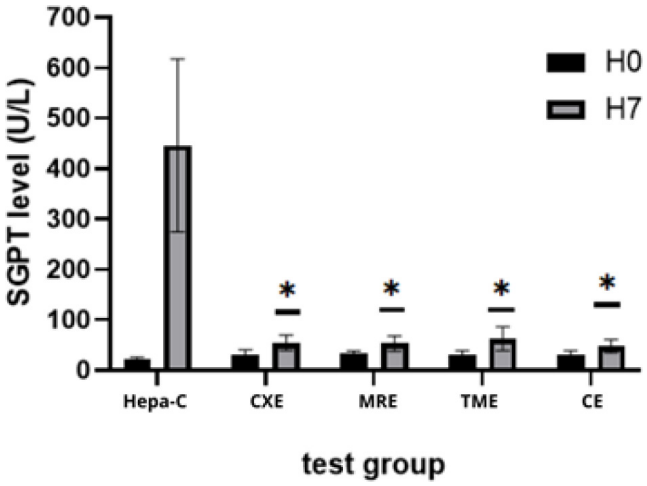
Table 1. Phytochemical screening test results of *C. xanthorrhiza*, Mangosteen rind, and tea mistletoe

Phytochemical Test	Reagent	Extract	Test Results (+/-)	Result
Flavonoid	Chloroform + UV 366	CXE	+	Intense yellow fluorescent colour under UV
		MRE	+	
		TME	+	
Polyphenols	$FeCl_3$	CXE	+	Blue-green colour
		MRE	+	
		TME	+	
Anthraquinone	Concentrated sulfuric acid + ammonia	CXE	+	Pink
		MRE	+	
		TME	+	

4.44%, respectively. These results satisfy the extract water content quality test, which requires a score of ≤ 10%. The results of the phytochemical screening show that all extracts contain flavonoids, polyphenols, and anthraquinones (Table 1).

3.2 Modelling Hepatotoxic with FDC ATDs

The baseline SGPT levels of all rats were within the normal range that is 29.64 ± 6.87 U/L (normal: 17.5-30.2 U/L). The SGPT levels in the Hepa-C group after being induced for 7 days with FDC ATDs showed SGPT levels of 446±171 U/L ($p<0.05$), indicating liver damage leading to a hepatotoxic state.



Hepa-C: Hepatotoxic Control; CXE: Curcuma Extract; MRE: Mangosteen Rind Extract; MTE: Mistletoe Leaf Extract; CE: Combination Extract. #: Significant difference with $p < 0.05$ compared to baseline, * significant difference with $p<0$. .05 compared to baseline, * significant difference with $p<0.05$ compared Hepa-C group (n = 5). The test used was Mann-Whitney (2-tailed).

Figure 1. SGPT level results.

3.3 SGPT Level

All extracts have the potential to significantly reduce SGPT levels ($p<0.05$) compared to the hepa-C group. The SGPT levels for CXE, MRE, TME, and CE were 54.2 ± 15.35; 52.8 ± 15.01; 62.4 ± 23.62; and 47.6 ± 12.76 U/L, respectively. Although this decrease has not yet reached normal SGPT levels, these results were confirmed with histopathological data and GSH levels (Figure 1).

3.4 The Results of Histopathological Observations and Quantitative Result

Histopathological testing confirmed that the Hepa-C group had an average total of 55.33 ± 2.52 damaged cells, above the normal cells average of 44.67 ± 2.52 ($p<0.05$). All extracts showed a reduced average count of damaged cells compared with Hepa-C ($p<0.05$), whereas the average total of normal cells exceeded that of Hepa-C ($p<0.05$). The CE group exhibited the lowest cell damage, with a total of 27.67 ± 2.08 damaged cells (Figure 2, 3 and Table 2). Pyknotic cells are a type of cell that undergoes chromatin condensation, resulting in a reduction in size, increasing density, and thickening of the cell nucleus. Karyorrhexis cells are a prolongation of the pyknosis state, in which the cell nucleus becomes pale and loses its original shape due to the dissolution of chromatin. Karyolytic cells are characterised by the rupture of the cell nucleus. Pyknosis cells, karyorrhexis, and karyolysis cells are processes that induce cell necrosis or death[28].

3.5 Percentage the Relative Liver-to-body Weight Ratio of the Rats

The increase in the percentage of relative liver organs in BB is directly proportional to the results of liver

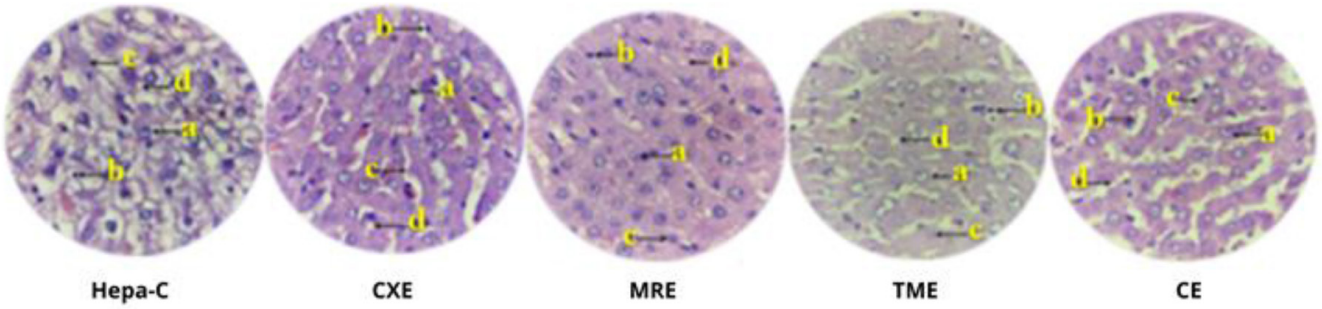
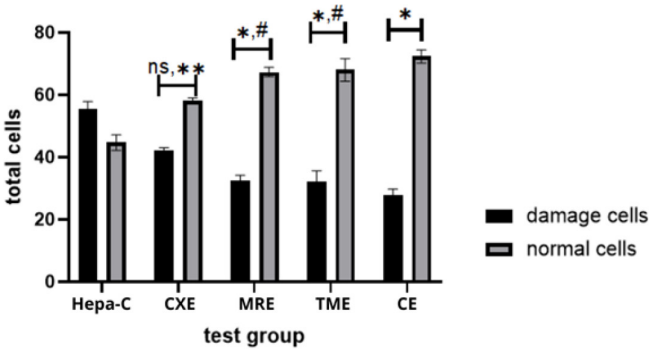


Figure 2. The results of histopathological observations of liver cells (magnification 1000 x). a. normal cells, b. pyknosis, c. karyorrhexis, d. Karyolysis.

histopathology (Figure 4). The comparison between the treatment group and the hepatotoxic control is statistically significant ($p<0.05$), as indicated by the percentage relative organ results. These result are consistent with the hypothesis that exposure to toxic agents can disrupt cell metabolism and induce cell swelling[29]. The percentage of a relative organ increases as a result of this cell enlargement.

3.6 Result of GSH Level in Rats

Compared to the CXE and MRE groups that received single extracts, the CE group showed the highest GSH levels. Nevertheless, this administration demonstrated not significant difference of GSH levels ($p>0.05$). The CXE group exhibited negligible GSH levels in comparison to the Hepa-C group ($p>0.05$) (Figure 5).



Hepa-C: Hepatotoxic Control; CXE: Curcuma Extract; MRE: Mangosteen Rind Extract; TME: Mistletoe Leaf Extract; CE: Combination Extract. *: There is a significant difference ($p<0.05$) compared to hepatotoxic control; **: There is a significant difference ($p<0.05$) compared to the combination group; #: no significant difference ($p>0.05$) compared to the combination group (n = 5).

Figure 3. Quantitative results of liver cell histopathology.

4. Discussion

The metabolic pathway of Isoniazid (INH) highlights a potential mechanism for idiosyncratic hepatotoxicity (Figure 6). Evaluation of INH metabolism indicates that its biotransformation *via* N-acetyltransferase (NAT) to acetyl isoniazid, followed by conversion to isonicotinic acid and monoacetylhydrazine, contributes significantly to the formation of hepatotoxic intermediates.

Monoacetylhydrazine undergoes further metabolic reactions to produce diacetylhydrazine, hydrazone, and oxidised hydrazine. Among these, the oxidised hydrazine metabolite exhibits a high degree of electrophilicity, making it susceptible to covalent binding to hepatocyte proteins. This covalent interaction has been evaluated as a crucial step in triggering immune-mediated liver injury, suggesting that monitoring the formation of this metabolite may serve as an early indicator of hepatotoxic risk. Furthermore, a comparative evaluation of these metabolic intermediates indicates that oxidised hydrazine plays a dominant role in hepatotoxic outcomes compared to the relatively benign isonicotinic acid and diacetylhydrazine, which are efficiently eliminated. These insights reinforce the importance of evaluating metabolic profiles in predicting and mitigating isoniazid-induced liver toxicity[30-32].

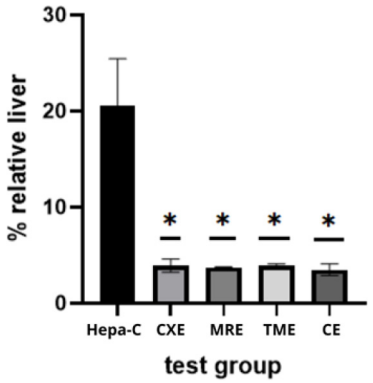
Pyrazinamide is known to cause dose-dependent hepatotoxicity. In the liver, pyrazinamide is metabolised *via* two distinct pathways. The first pathway involves amidase, which converts pyrazinamide to Pyrazinoic Acid (PA), a metabolite believed to contribute to liver damage. The second pathway involves Xanthine Oxidase (XO), which metabolises pyrazinamide to

Table 2. Tukey HSD analysis results of liver cell histopathology (n=5)

(I) Group	(J) Group	Damage Cells		Normal Cells	
		Mean Difference (I-J)	Significancy (p)	Mean Difference (I-J)	Significancy (p)
Hepa-C	CXE	13.333*	0.000	-13.333*	0.000
	ME	22.667*	0.000	-22.667*	0.000
	TE	23.333*	0.000	-23.333*	0.000
CE	Hepa-C	-27.667#	0.000	27.667#	0.000
	CXE	-14.333#	0.000	14.333#	0.000
	ME	-5.000#	0.025	5.000#	0.025
	TE	-4.333#	0.045	4.333#	0.045

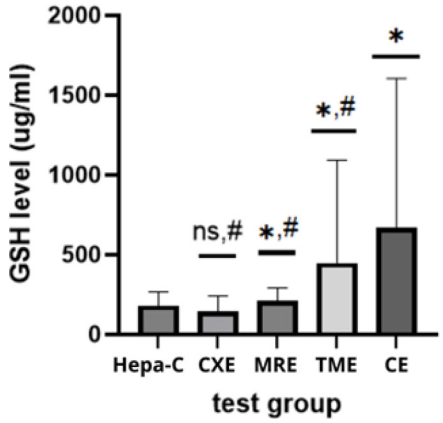
*There is significant different ($p<0.05$) compared with Hepa-C. # there is significant different ($p<0.05$) compared with CE.

5-hydroxy-pyrazinamide (5-OH-PZA), followed by further metabolism by amidase to 5-hydroxy-pyrazinoic acid (5-OH-PA). Both PA and 5-OH-PA are suspected hepatotoxins[33-35]. Although the mechanism of rifampin hepatotoxicity remains unclear, several mechanisms have been proposed, including its role in promoting the breakdown of isoniazid to hydrazine, inducing mitochondrial stress, causing hepatocellular



Hepa-C: Hepatotoxic Control; CXE : *C. xanthorrhiza* Extract; MRE : Mangosteen Rind Extract; TME: Tea Mistletoe Extract; CE: Combination Extract.
*significant difference ($p<0.05$) compared to Hepa-C (n = 5).

Figure 4. % Relative liver-body weight.



Hepa-C: Hepatotoxic Control; CXE : *C. xanthorrhiza* Extract; MRE : Mangosteen Rind Extract; TME : Tea Mistletoe Extract; CE: Combination Extract. ns: no significant difference ($p>0.05$) compared to hepatotoxic control; *: there is a significant difference ($p<0.05$) compared to hepatotoxic control; #: no significant difference ($p>0.05$) compared to combination group (n = 5).

Figure 5. GSH levels results.

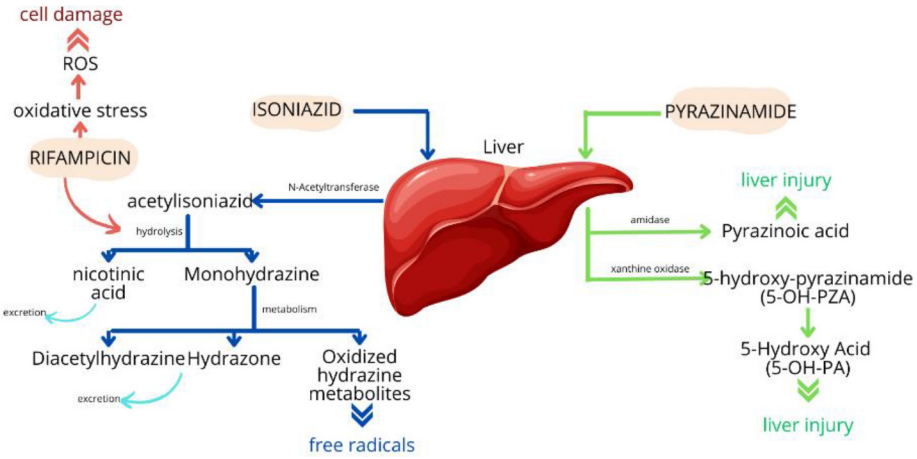


Figure 6. Hepatotoxic mechanism of ATDs.

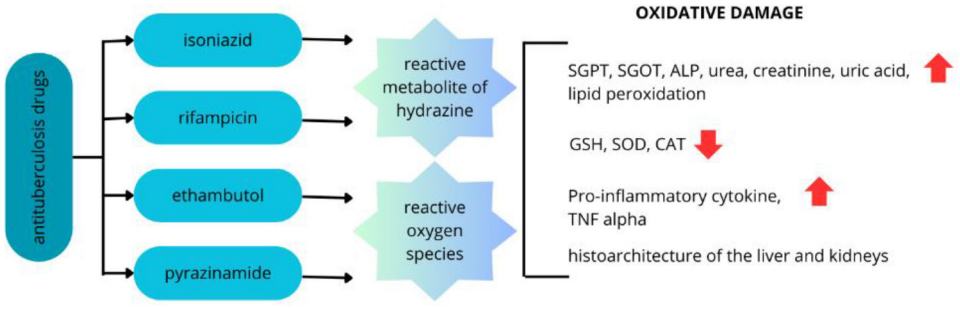


Figure 7. Biomarkers of oxidative damage due to FDC ATDs induction.

apoptosis, steatosis, and cholestasis. Ethambutol is rarely associated with hepatotoxicity, and the mechanism of liver damage remains unknown. The details of ATDs hepatotoxic mechanism is given in Figure 7.

In this study, the hepatoprotective effects of CXE, MRE, and TME were evaluated based on their antioxidant potential, ability to modulate endogenous enzyme systems, and anti-inflammatory actions. CXE demonstrated significant hepatoprotective efficacy. Its active components, including gingerols, shogaols, and zingerone, possess potent antioxidant capacity. The extracts exhibited radical-scavenging activity and increased levels of endogenous antioxidant enzymes such as Superoxide Dismutase (SOD), Glutathione Peroxidase (GPx), and Catalase (CAT), indicating enhanced cellular defense against Reactive Oxygen Species (ROS). Evaluation of lipid peroxidation markers revealed decreased Malondialdehyde (MDA) levels, supporting its membrane-stabilising effect. Furthermore, gingerols were shown to activate the Nrf2/ARE pathway, increasing the expression of antioxidant response genes, thus strengthening the role of CXE in counteracting oxidative damage[36-38].

Evaluation of MRE revealed the presence of potent antioxidant xanthones, particularly α-mangostin, γ-mangostin, and garcinone E. These compounds exhibit potent radical scavenging capacity and inhibition of lipid peroxidation through membrane lipid stabilisation. Mechanistically, MRE modulates the Nrf2-ARE signalling pathway, increasing the expression of detoxification enzymes such as Heme Oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase 1 (NQO1), and Glutathione-S-Transferase (GST). Furthermore, γ-mangostin has been shown to inhibit NADPH Oxidase (NOX), reduce ROS production, and exert anti-inflammatory effects by down regulating NF-**κB** and its downstream targets, including TNF-α and IL-6. This evaluation indicates that MRE provides comprehensive protection against oxidative liver damage and inflammation[39-42].

TME also demonstrated hepatoprotective potential in this evaluation. Its polyphenolic compounds, such as quercetin, rutin, kaempferol, tannins, and phenolic acids, contribute to its antioxidant properties. Radical scavenging assays confirmed the ability of TME to neutralise superoxide and hydroxyl radicals. Furthermore, TME effectively chelates pro-oxidant metal ions such as Fe^{2} and Cu^{2+}, thereby reducing the formation of hydroxyl radicals through the Fenton reaction. This extract increases the activity of endogenous antioxidant enzymes (SOD, CAT, GPx) and activates the Keap1-Nrf2 pathway, primarily through the action of kaempferol, leading to increased expression of antioxidant enzyme genes[43,44].

This study evaluated several liver injury biomarkers to assess oxidative damage caused by Fixed-Dose Combination (FDC) antituberculosis drugs (OTD), including Serum Glutamic Pyruvic Transaminase (SGPT), glutathione (GSH), and liver histopathology (Figure 7). SGPT levels were significantly increased in the Hepa-C group (446 ± 171.26 U/L) compared to the treatment group (CXE: 54.2 ± 15.35; MRE: 52.8 ± 15.01; TME: 62.4 ± 23.62; CE: 47.6 ± 12.76), indicating hepatocyte membrane protection. Similarly, GSH levels in the Hepa-C group decreased (93.45 ± 4.34), while increased in the extract group (CXE: 154.73 ± 97.49; MRE: 209.97 ± 82.99; TME: 434.82 ± 620.40; CE: 670.88 ± 935.18), indicating restoration of antioxidant capacity 1.38.46. Histological differences supported these findings, with the highest number of damaged cells in Hepa-C (55.33 ± 2.52) and lower in the extract group (CXE: 42.00 ± 1.00; MRE: 32.67 ± 1.53; TME: 32.00 ± 3.60; CE: 27.67 ± 2.08). These findings align with previous hepatoprotective studies using *silymarin* and *curcumin*, which both demonstrated increased GSH levels, decreased MDA, Nrf2 activation, and NF-**κB** suppression[45]. The mechanisms demonstrated by CXE, MRE, and TME including increased antioxidant enzyme activity and restoration of hepatocyte structural integrity show similarities to the hepatoprotective profiles of these reference plants, thus strengthening the biological relevance of this study's findings[1,38,46].

This study has several limitations, including the relatively small sample size, the lack of use of more specific mechanistic biomarkers such as detection of hydrazine protein adducts, markers of mitochondrial stress, or profiles of CYP enzymes involved in the bioactivation of toxic metabolites. Furthermore, the pharmacokinetics of the extracts were not assessed, thus, the dose-effect relationship and potential interactions with anti-TB drug regimens cannot be comprehensively elucidated. Overall, the CXE, MRE, TME, and CE extracts demonstrated the ability to maintain hepatocyte integrity and suppress anti-TB

drug-induced oxidative stress. The most consistent effect was seen in the CE group, although it was not statistically superior to the single extract, so further studies are needed to optimise the dose, test for synergistic effects, conduct direct comparisons with standard hepatoprotectant, and evaluate more specific molecular biomarkers to clarify its hepatoprotective pathway of action.

5. Conclusion

This study demonstrated that the extracts of *C. xanthorrhiza* (CXE), Mangosteen Rind (MRE), and Tea Mistletoe (TME) possess hepatoprotective activity, as evidenced by their ability to reduce SGPT levels, increase GSH concentrations, and preserve liver histological architecture following FDC anti-tuberculosis drug-induced hepatotoxicity. Their antioxidant properties to mitigating oxidative stress were contributed by presence of secondary metabolites such as flavonoid, polyphenol, and anthraquinones. The enhancement of the endogenous antioxidant defence, particularly through the GSH pathway, played a crucial role in restoring redox balance and maintaining hepatocyte integrity. These findings provide a preclinical evaluation supporting the potential use of these extracts as complementary hepatoprotective agents against drug-induced liver injury.

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8. Ethical Committee Approval

The Health Research Ethics Committee of the UMS Faculty of Medicine has approved this investigation based on an ethical feasibility letter with the number 5263/B.1/KEPK-FKUMS/VIII/2024.

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Author Contribution

Authors have made substantive intellectual contribution to the content of this manuscript. Arifah Sri Wahyuni, Arini Fadhilah, Ajeng Rahmadhani, Diski Wahyu Wijianto, and Fazleen Izzany Abu Bakar have contribution in concept and design, data acquisition, data analysis, drafting manuscript, statistical analysis, technical or material support, and final approval. All authors have read and agreed to the published version of the manuscript.