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Current Progress in Developing Plant Extract-Based Hepatoprotective Drugs to Prevent Drug-Induced Liver Injury During Tuberculosis Treatment: A Literature Review

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ABSTRACT

Introduction: Anti-tuberculosis treatment (ATT) can cause drug-induced liver injury. This complication leads to disruption of tuberculosis treatment. Therefore, plant extract-based is useful in a way to prevent drug-induced liver injury due to ATT.
Methods: This review source came from PubMed and Google Scholar. We found 59 articles with the keywords "drug-induced liver injury" AND "hepatotoxicity" in the range 2014-2024. We selected 12 articles to be reviewed in this article.
Result: Plant extract-based in this article has several mechanisms to prevent drug-induced liver injury due to ATT. All of them contain high antioxidants. Silymarin works by blocking the effects of the enzymes catalase and glutathione peroxidase, as well as suppressing the action of lipid peroxidase which causes liver damage. Jujube, Lasianthera africana, and Telfairia occidentalis can neutralize free radicals. Trapa natans and Bacopa monnieri work from the glutathione (GSH) pathway. Bacoside and Tamarix gallica mechanisms to prevent liver injury are still unknown. Most of the herbs can decrease levels of AST, ALT, and ALP as biomarkers of liver injury significantly.
Conclusion: Many plant extracts have the potential to prevent the incidence of drug-induced liver injury caused by ATT both in animal models and clinical trials. However, adequate dosing and sample size are required to make sure that the effects are significant.

Keywords: drug-induced liver injury; isoniazid; plant extract-based; rifampisin

INTRODUCTION

Tuberculosis is an infectious disease that affects the lower respiratory tract, especially the lungs[1]. The etiology of tuberculosis is *Mycobacterium tuberculosis*[2]. Tuberculosis can spread through droplets in the air[3]. According to the World Health Organization (WHO), 10.6 million people have tuberculosis with 1.3 million cases of mortality due to tuberculosis each year[4]. Typical clinical manifestations of tuberculosis are a chronic cough that lasts more than two weeks with hemoptysis, loss of appetite also having weight loss, fever that is less than 38.5°C, and night sweats[5]. The diagnosis of tuberculosis is made by chest x-ray and sputum tests to find the acid-fast bacillus as the cause of tuberculosis[6].

Ending tuberculosis is one of the sustainable development goals (SDGs) of the World Health Organization[7]. The first-line anti-tuberculosis drugs consist of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol[8]. Tuberculosis treatment is separated into an intensive phase and a continuation phase[9]. Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol are given for two months during the intensive phase, whereas the continuation phase only includes Rifampicin and Isoniazid in the regimen for four months[8]. The first-line anti-tuberculosis drugs have a treatment success rate of up to 95%[10]. Unfortunately, first-line anti-tuberculosis drugs have side effects on the liver. All anti-tuberculosis drugs have a potential for hepatotoxicity that causes drug-induced liver injury[11]. Drug-induced liver injury cases due to anti-tuberculosis drugs are reported to reach 28%[12]. It can have a detrimental effect on the course of treatment as the treatment needs to be halted, causing a failure of tuberculosis treatment[11]. Therefore, finding a way to prevent drug-induced liver injury with hepatoprotective drugs for tuberculosis patients is important.

Previous studies have shown that plant extracts have some potential in limiting drug-induced liver injury caused by anti-tuberculosis drugs, even though the results are either under debate or need further study because of the small sample size[13,14]. Therefore, hepatoprotective drugs for anti-tuberculosis drugs based on plant extract are interesting to research. This review aims to evaluate the current progress in developing hepatoprotective agents for anti-tuberculosis medicines obtained from plant extracts.

METHOD

This study is a narrative review aiming to evaluate current evidence on the use of plant extract-based hepatoprotective agents to prevent anti-tuberculosis drug-induced liver injury (DILI). We conducted a comprehensive search using PubMed and Google Scholar, filtering out the database from the last 10 years between May 2014 and May 2024. Some inclusion criteria we used for article selection were original articles published in English with full text available, studies involving either clinical trials or animal models, study subjects suffered from tuberculosis without any comorbidities (for example HIV/AIDS), no resistance to tuberculosis treatment (MDR or XDR), using herbs for DILI prevention. Articles were excluded if they were review articles, editorials, or commentaries, or did not focus on hepatoprotection using natural plant-based interventions or lacked liver toxicity outcome data related to tuberculosis treatment. Keywords used were: ‘drug-induced liver injury’, ’hepatotoxicity’, ’plant extract’, ’anti-tuberculosis drugs’, and Boolean operators such as AND/OR were applied accordingly. We used Pubmed search term as follow: ((“drug-induced liver injury” [Title/Abstract]) AND (“plant extract” OR “herbal”)) AND (“tuberculosis” OR “anti-TB drugs”). We found 59 articles that discussed hepatoprotection for tuberculosis treatment, 14 articles which we selected based on inclusion and exclusion criteria, and then we excluded 2 articles that weren’t relevant to the topic and 1 article that did not report the significant difference of liver enzymes.

RESULT

Overall Summary of Included Studies

There was a total of 11 articles we analyzed for this narrative review. We found those articles set up a control group, that treated with anti-tuberculosis treatments only, mostly rifampicin and isoniazid, and the experimental groups, which were given plant-based extract along with anti-tuberculosis treatments. Several articles have more than two experimental groups to examine the effects of different doses of the herbs used. The means of the studies show a significant decrease in the levels of AST, ALT, and ALP. The summarized studies included in this review are shown in Table 1.

Table 1 Research of plant extract-based hepatoprotective drugs that prevent drug-induced liver injury

No	Author, Year	Herbs Used	Methods	Anti-Tuberculosis Treatment Used	Summary
1	Talebi A, et al., 2023[15]	*Silybum marianum*	Patients that were in experimental group (n = 16) received Silymarin 150 mg twice daily for 14 days.	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide	At the end of the second-week experiment, the experimental group showed significantly lower serum levels of AST ($p < 0.05$), ALT ($p < 0.05$), and ALP ($p < 0.01$). No one in the experimental group developed anti-tuberculosis drug-induced hepatotoxicity, therefore silymarin has the potential as a hepatoprotective drug.
2	Maddahi SZ, et al., 2022[16]	*Ziziphus jujuba*	Patients in the experimental group (n = 8) were given Jujube syrup 5ml twice daily, 20 minutes after breakfast and 20 minutes after dinner, for 4 weeks. Liver enzymes were regularly checked every 2 weeks.	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide	0 cases in the experimental group experienced anti-tuberculosis drug-induced liver injury. In the second week, the serum of AST ($p < 0.05$), ALT ($p > 0.05$), and ALP ($p > 0.05$) decreased in the experimental group. There was also a decline that occurred in the fourth week of the AST ($p > 0.05$), ALT ($p > 0.05$), and ALP ($p > 0.05$).
3	Sabina EP, et al., 2019[17]	*Bacopa monnieri*	Female Wistar albino rats (n = 24) were divided into 4 groups, contained 6 rats in each group. Group II were treated with Rifampicin, Isoniazid, and given Bacoside extract at a dose of 10 mg/kg/ body weight for 28 days.	Isoniazid and Rifampicin	The effect of bacoside made a significant decrease in AST, ALT, and ALP serum ($p < 0.05$) compared with the control group that was only given Isoniazid and Rifampicin.
4	Nwidu LL, et al., 2018[18]	*Lasianthera africana*	Male and female Wistar rats (n = 36) were divided into control group and experimental group. In experimental group, Wistar rats received RIF, INH, and also HALA for 1 g/kg/body weight for 28 days.	Isoniazid and Rifampicin	The experimental group that was given HALA extract experienced a decrease in the level of ALP, AST, and ALT ($p < 0.01$) also total cholesterol, total triglycerides, low-density lipoprotein, and total bilirubin ($p < 0.01$). The results prove that *L. africana* can be used as a hepatoprotective drug for RIF-INH-treated management

No	Author, Year	Herbs Used	Methods	Anti-Tuberculosis Treatment Used	Summary
5	Hussain T, et al., 2018[19]	*Trapa natans*	There were 5 groups of male Wistar rats (n = 30), with 6 rats in each group. Group III and IV were administered with *T. natans* fruit peel extract for 200 mg/kg/body weight and 400 mg/kg/body weight for 15 days.	Isoniazid and Rifampicin	Group III that were given *T. natans* (200 mg/kg/body weight) experienced a significant reduction in AST ($p < 0.01$), ALT ($p < 0.01$), and ALP ($p < 0.01$). While as, Group IV, that were given T. natans (400 mg/kg/body weight) also experienced a significant decrease in AST ($p < 0.01$), ALT ($p < 0.01$), and ALP ($p < 0.01$)
6	Nwidu LL, et al., 2019[20]	*Telfaira occidentalis*	Male Wistar rats (n = 15) were set up into 5 groups. Group III, IV, and V administrated with Isoniazid, Rifampicin, and various dose of *T. occidentalis* (125 mg/kg/body weight, 250 mg/kg/body weight, and 500 mg/kg/body weight) for 60 days.	Isoniazid and Rifampicin	The effects of *Telfairia occidentalis* (125-500mg/kg) significantly decreased the level of ALP, AST, and ALT ($p < 0.01$) in the experimental groups compared with the control groups.
7	Evan Prince S, et al., 2016[21]	*Bacopa monnieri*	There were 5 separate groups of female Wistar albino rats (n = 30), each with 6 rats were set up. Group III was treated with *B. monnieri* at a dose of 500 mg/kg/body weight orally up to 28 days.	Isoniazid and Rifampicin	The Group III that was administrated with *Bacopa monnieri* showed a significant decrease in ALT ($p < 0.05$), AST ($p < 0.05$), and ALP ($p < 0.05$) compared with the control group that was not given any hepatoprotection.
8	Urfi MK, et al., 2018[22]	*Tamarix gallica*	Twenty-five male Sprague Dawley rats divided into 5 groups, with each contained 5 rats. Group III and IV were administered 100 mg/kg/body weight and 200 mg/kg/body weight of *Tamarix gallica* suspension for 28 days.	Isoniazid and Rifampicin	Group III that received *Tamarix gallica* extract for 100 mg/kg/body weight experienced a decrease of the levels ALP ($p < 0.05$), ALT ($p > 0.05$), and AST ($p > 0.05$). Meanwhile, Group IV that received *Tamarix gallica* extract for 200 mg/kg/body weight experienced a highly significant decrease of the levels ALP ($p < 0.01$), ALT ($p < 0.01$), and AST ($p < 0.01$).

No	Author, Year	Herbs Used	Methods	Anti-Tuberculosis Treatment Used	Summary
9	Emrani Zahra, et al., 2016[23]	*Zingiber officinale*	Sixty-nine patients were randomly divided into control and experimental groups. The experimental group (n = 30) received 500mg ginger once daily for 4 weeks.	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide	Ginger administration prevented the incidence of hepatotoxicity, proved by the decreased level of AST ($p < 0.05$), ALT ($p > 0.05$), and ALP ($p > 0.05$).
10	Luangchosiri C, et al., 2015[25]	*Silybum marianum*	Twenty-seven patients in experimental group were received 140 mg tablet of Silymarin three times a day along with anti-tuberculosis treatments for 4 weeks.	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide	Patients in experimental groups had a significantly lower risk of anti-tuberculosis-DILI than the control group receiving placebo ($p < 0.05$). This result was supported by data on decreased liver enzymes ALT ($p < 0.05$), AST ($p > 0.05$), and ALP ($p > 0.05$)
11	Heo E, et al., 2017[26]	*Silybum marianum*	Forty-five patients were given 140 mg Silymarin twice daily along with anti-tuberculosis treatments for 8 weeks.	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide	In this study, Silymarin didn't show any significant effect in preventing anti-tuberculosis-DILI, based on the results of ALP, and ALT ($p > 0.05$) at the end of eight week.

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; RIF = rifampicin; INH = isoniazid; HALA = the hepatoprotective effects of hot aqueous *L. africana.*

Differences between Human and Animal Studies

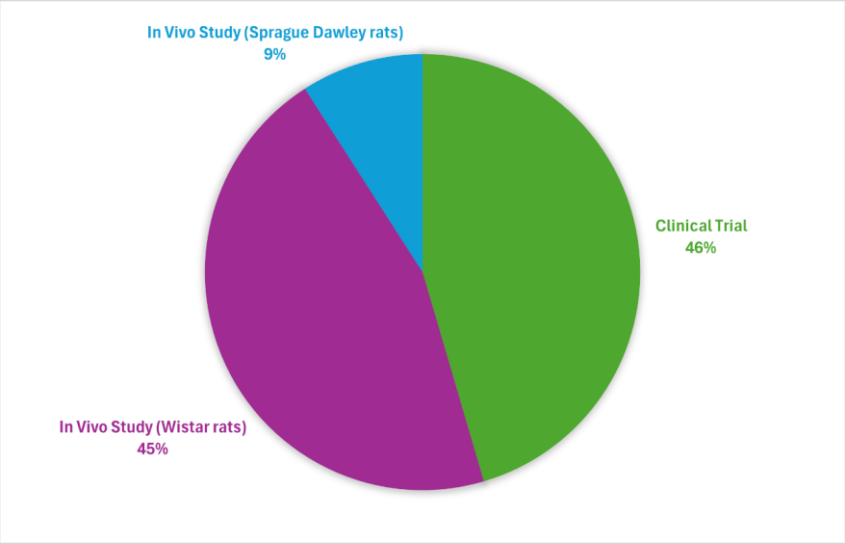

Figure 1. Research methods of the articles analyzed

From the 11 articles we analyzed, 5 articles used clinical trials as research methods with humans as subjects. Those clinical trials were held in Al-Zahra Hospital (Iran), Urban Health Centers and Rural Health Houses (Iran), Imam Khomeini Hospital Complex (Iran), Boramae Medical Center (Korea), and Ramathibodi Hospital (Thailand). The rest 6 articles used animals for an in vivo study. Most of the studies chose Wistar rats as study subjects, either male or female. Only one article used male Sprague Dawley rats as study subjects. The percentage of the study methods (animal or human study) used in this review is shown in Figure 1.

Based on Table 1 findings, animal studies consistently demonstrate marked hepatoprotective effects of various plant extracts such as *Bacopa monnieri*, *Lasianthera africana*, *Trapa natans*, *Telfairia occidentalis*, and *Tamarix gallica* against liver injury caused by anti-tuberculosis drugs, as evident in significant reduction in liver enzyme levels (AST, ALT, ALP) with high statistical significance (mostly $p < 0.01$). These studies typically involve controlled dosing, consistent duration, and the ability to quantify histological or biochemical changes with high precision. In contrast, human studies/clinical trials show more variable outcomes. Some clinical trials involving *Silybum marianum*, *Ziziphus jujuba*, and *Zingiber officinale* yield reduced risk of hepatotoxicity or restoration of liver enzymes, but others, such as the study by Heo et al., found no significant improvement. This heterogeneity can be attributed to greater biological and environmental heterogeneity within human subjects, different dosing regimens, and confounding clinical factors. Overall, while preclinical animal models solidly established hepatoprotective potential, human trials are inconclusive, highlighting the need for larger, better-designed clinical trials.

Effect on Liver Enzymes

Based on the data we had analyzed, study group numbers 4, 5A, 5B, 6A, 6B, 6C, and 8B showed a highly significant ($p < 0.01$) decrease of serum AST, ALT, and ALP after being given with extract. Then, study groups 3 and 7 showed a significant ($p < 0.05$) decrease in serum AST, ALT, and ALP. However, study groups 2B and 11 did not show any significant ($p > 0.05$) decrease in serum AST, ALT, and ALP. The rest of the study groups (1, 2A, 8A, 9, and 10) showed varying results of decreasing serum AST, ALT, and ALP. The summarized effectiveness of herbs on AST, ALT, and ALP levels is shown in Figure 2.

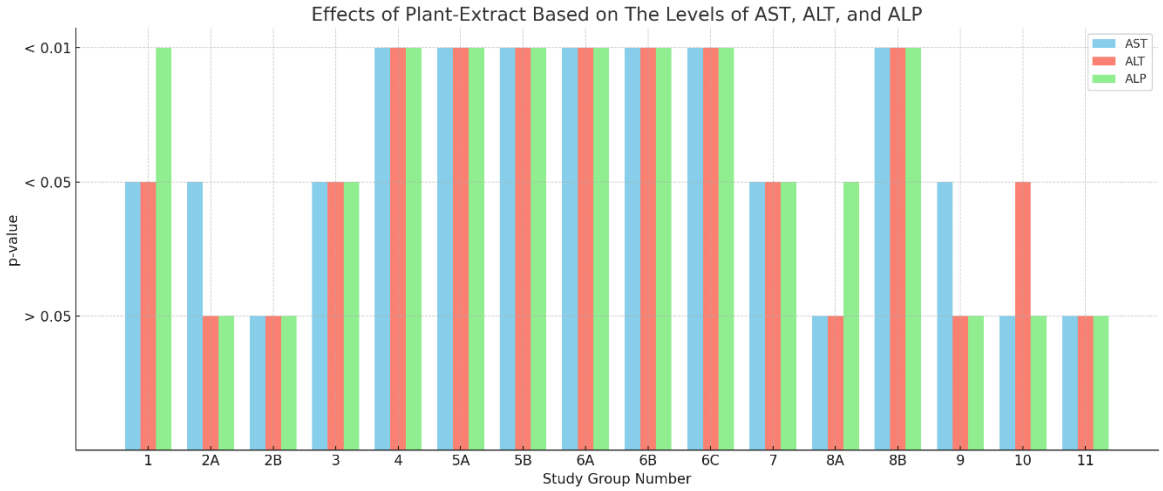

Figure 2. Summary of herbs' effectiveness to prevent anti-tuberculosis-DILI based on p-value

Y axis (p-value) : > 0.05 = non-significant; < 0.05 = significant; < 0.01 = highly significant
X axis (study group number) : 1 = *Silybum marianum* 150mg bid; 2A = *Ziziphus jujuba* 5ml bid week 2; 2B = *Ziziphus jujuba* 5ml bid week 4; 3 = *Bacopa monnieri* 10 mg/kg/body weight; 4 = *Lasianthera africana* 1

g/kg/body weight; 5A = *Trapa natans* 200 mg/kg/body weight; 5B = *Trapa natans* 400 mg/kg/body weight; 6A = *Telfaira occidentalis* 125 mg/kg/body weight; 6B = *Telfaira occidentalis* 250 mg/kg/body weight; 6C = *Telfaira occidentalis* 500 mg/kg/body weight; 7 = *Bacopa monnieri* 500 mg/kg/body weight; 8A = *Tamarix gallica* 100 mg/kg/body weight; 8B = *Tamarix gallica* 200 mg/kg/body weight; 9 = *Zingiber officinale* 500 mg/kg/body weight; 10 = *Silybum marianum* 140 tid; 11 = *Silybum marianum* 140 bid.

Herbs with the Strongest Hepatoprotective Effect

From the 11 articles we analyzed, the most widely used plant species for hepatoprotection was *Silybum marianum*, known as Silymarin or Milk Thistle, followed by *Bacopa monnieri*, which is known as Bacoside. A total of three articles used *Silybum marianum*, two articles used *Bacopa monnieri*, while other species were only used in one article. The summary of herb species used as hepatoprotectors in anti-tuberculosis DILI prevention is shown in Figure 3.

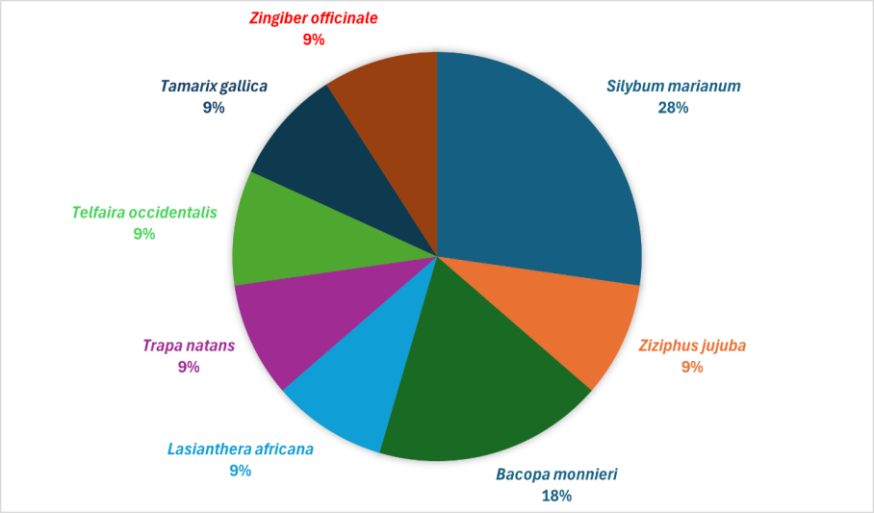

Figure 3. Species of herbs that were used as hepatoprotection for anti-tuberculosis-DILI prevention

Most herbs have flavonoids as active compounds to prevent DILI. Every species contains different types of flavonoids with antioxidant effects. *Silybum marianum* contains silibinin, silydianin, and silychristin. *Ziziphus jujuba* contains quercetin and kaempferol. Flavonoids that are in *Bacopa monnieri* are bacopasides, brahmine, and herpestine. Then, flavonoids that exist in *Zingiber officinale* are 6-gingerol, shogaol, and zingerone. While *Lasianthera africana, Trapa natans,* and *Tamarix gallica* contain flavonoid types that haven't been identified.

Silybum marianum (silymarin) and *Bacopa monnieri* demonstrate the strongest hepatoprotective effects. *Silybum marianum* showed consistent reductions in liver enzymes (AST, ALT, ALP) and significantly prevented DILI in two human studies, although one study reported no significant benefit, possibly due to longer treatment duration or patient variability. *Bacopa monnieri* showed robust hepatoprotection in two well-controlled animal studies, with significant decreases in AST, ALT, and ALP ($p < 0.05$) when administered alongside anti-TB drugs. Additionally, Trapa natans and Telfairia occidentalis also demonstrated potent dose-dependent enzyme reductions ($p < 0.01$) in animal models, further supporting their hepatoprotective potential. These herbs consistently outperformed others in both magnitude of liver enzyme reduction and statistical significance.

DISCUSSION

Drug-induced liver injury is a serious side effect of anti-tuberculosis therapy[27]. Multiple pathways cause liver injury due to Rifampicin[28]. Rifampicin binds with the pregnane X receptor (PXR), activating cytochrome P450 and other drug-metabolizing enzymes such as CYP2B6, 2C9, 2C19, and

3A4[29]. Induction of those enzymes is dose-dependent, where higher doses (more than 442.5mg/kg) of Rifampicin stimulate higher activity of P450 enzymes[30]. The activation of those enzymes causes damage in liver cells either by direct effect of oxidative stress in mitochondria or accumulation of toxic byproducts[28]. Interestingly, Rifampicin also causes up-regulation of peroxisome proliferator-activated receptor-γ (PPARγ) in the hepatocytes[31]. Activation of those receptors causes several proteins to be upregulated as well[31]. Among them, one of the most significant upregulated proteins is perilipin, which covers lipid droplets in adipocytes with a phospholipid monolayer and is involved in lipid metabolism, including lipid droplet formation and metabolism[32]. Lipolysis is known to be suppressed by perilipin, which prevents the utilization of fatty acid for metabolism and causes it to accumulate in the liver[33]. A prior study demonstrated that perilipin expression influences the development of lipid droplets in hepatocytes and tends to increase in response to the hepatocyte lipid content of the fatty liver in humans[32]. On the other hand, Pyrazinamide tends to deplete the storage of hepatic glutathione, a key antioxidant compound that protects the liver from free radicals[34]. Our immune cells can also exacerbate the damage caused by drugs by reacting with damage-associated molecular patterns released from damaged hepatocytes[35]. Therefore, preventing anti-tuberculosis drug-induced liver injury requires a strong antioxidant and immunomodulatory agent.

Silymarin (*Silybum marianum*), better known as Milk Thistle, is one of the plant extracts that has been known to have hepatoprotective effects[13]. Silymarin contains a flavonoid which acts as an antioxidant[36]. Silymarin works by blocking the effects of the enzymes catalase and glutathione peroxidase, as well as suppressing the action of lipid peroxidase which causes liver damage[37]. Silymarin can suppress liver damage optimally, as indicated by a significant reduction in AST, ALT, and ALP levels[25]. However, another study showed that the effect of Silymarin is not very significant[26]. This might happen because Silymarin has poor pharmacokinetics, only 20-50% of the extract can be absorbed by the digestive system[37].

Other herbs that are included in this study are Jujube, *Lasianthera africana*, and *Telfairia occidentalis*[16,18,20]. Like Silymarin, they also yield significant hepatoprotective ability. This attribute is caused by the high content of phenolic compounds in their extract, which can act as an antioxidant due to its ability to donate electrons from hydroxyl groups to neutralize free radicals, therefore preventing rifampicin and isoniazid from causing damage in liver cells[16,18,20].

Hepatoprotective agents can also work from other pathways such as glutathione (GSH)[28]. As we all know, GSH is a vital antioxidant compound that is naturally produced in the liver which works as a natural antioxidant in our body[38]. Depletion of this compound significantly increases our chance of having severe liver injury due to oxidative stress[28]. Compounds that utilize this pathway are *Trapa natans* and *Bacopa monnieri* extracts[19,21]. Administration of those compounds significantly increases hepatic GSH content, apart from ameliorating the level of serum ALT and AST as well[19,21].

Apart from reducing AST, ALT, and ALP, *Bacopa monnieri* and *Tamarix gallica* also have effects on body weight and total protein[17,22]. The rats that were given INH and RIF, then treated with *Bacopa monnieri* or *Tamarix gallica*, experienced enhancement of body weight as same as the normal group, far different compared with the hepatotoxic groups[17,22]. Also, the levels of total protein in the Bacoside-treated rats group were elevating[17]. Although the mechanism is still unknown, *Bacopa monnieri* and *Tamarix gallica* still have the potential as a hepatoprotective drug [17,22].

Among 11 studies explored in this literature review, 6 studies used animals while 5 other studies used humans as subjects. Further studies need to be conducted to confirm the insignificant results found in 2 studies (Graph 3).

CONCLUSION

In conclusion, plant extract might provide some benefits in preventing drug-induced liver injury caused by ATT, even though clinical trials with large sample populations and good quality are needed to further prove this benefit. *Silybum marianum, Ziziphus jujuba, Bacopa monnieri, Lasianthera africana, Trapa natans, Telfaira occidentalis, Tamarix gallica,* and *Zingiber officinale,*are proven to reduce damage in the liver by decreasing liver enzymes and GSH content. Thus, they could be considered as complementary therapy for preventing and or curating drug-induced liver injury caused by tuberculosis treatment.

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CONFLICT OF INTEREST

Authors declared no conflict of interest.

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