Efficacy of hepatoprotector jamu formula (combination of *Curcuma longa*, *Curcuma xanthorrhiza*, and *Taraxacum officinale*) compared to *Fructus schizandrae* extract in mild liver injury: a randomized controlled trial

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Abstract. The prevalence of impaired liver function in developing countries is increasing. Indonesia has several traditional medicines that can be used as alternative treatments for liver dysfunction. The aim of this study was to determine the efficacy of hepatoprotector jamu formula (combination of *Curcuma longa*, *Curcuma xanthorrhiza*, and *Taraxacum officinale*) compared to *Fructus schizandrae* fruit extract for treating mild liver injury. This study was a RCT using parallel open label design which involved 60 subjects for 42 days of intervention. The parameters used to evaluate efficacy were Serum Glutamic Pyruvic Transaminase (SGPT) and Serum Glutamic Oxaloacetic Transaminase (SGOT). There was a significant difference of average SGPT levels on day 21 and day 42 compared to day 0 in both hepatoprotector jamu group and *Fructus Schizandrae* extract group (p < 0.001). Compared to the baseline, there were a significant difference of average SGOT levels on the follow up days in hepatoprotector jamu group (p = 0.023 on day 21; p = 0.003 on day 42) as well as *Fructus Schizandrae* extract group (p = 0.028 on day 21; p = 0.042 on day 42. The efficacy of hepatoprotector jamu formula was comparable to *Fructus schizandrae* extract in improving mild liver injury.

1. Introduction

The liver is the largest internal organ in the body, normally weighing around 1.6 kg in men and 1.4 kg in women. Functions of the liver include metabolism of carbohydrate, fat, protein, bilirubin, drugs, and several hormones; synthesis of cholesterol, bile, plasma protein, clotting factors, glucose, amino acid, and urea; regulating blood sugar; storage of glycogen and fat soluble vitamins; as well as immunity [1]. At the same time, this organ acts as a filter that has to take up potentially damaging substances like microorganisms, toxins, or drugs delivered through the portal blood circulation so that it is very prone to injury [2]. The most used parameters for liver disease screening tests are SGPT and SGOT. Both SGPT and SGOT are serum enzymes which are sensitive to liver cell damage. The increase of SGPT and/or SGOT enzymes ≥ 2x upper limit of normal is an indicator for liver cell disorders. Liver cell damage can occur due to viral infection, alcohol, metabolic syndrome, autoimmune disease, drugs, or toxins that potentially lead to hepatitis, fatty liver, cirrhosis, and liver cancer[3].
Considering the great burden of liver disease in many countries, we need an integrated approach including the availability of medicines for treatment [4]. Currently the availability of modern drugs that are effective in stimulating liver function, protecting the liver from damage, or helping to regenerate liver cells are still limited. Meanwhile, the discoveries of new compounds in medicinal plants continue to expand, including active substances to combat liver disease which are often referred as hepatoprotectors [5].

Indonesian traditional medicine, known as *jamu*, is one of Indonesia's cultural heritages that is considered to have medicinal purposes. The diversity of herbal medicine in Indonesia requires further research to clearly prove its safety and efficacy [6]. The Jamu Sanctification Program is a breakthrough effort in accelerating herbal medicine research based on health services conducted by medical professionals. The results of herbal medicine scientific research can be used as evidence-based medicine so that *jamu* can be included in the formal health services [7].

Preclinical research found that herbal concoction consisting of *Curcuma longa* rhizomes, *Curcuma xanthorrhiza* rhizomes, and *Taraxacum officinale* leaves given to mice along with paracetamol at a dose of 500 mg/kg body weight for 7 days has a hepatoprotective effect by inhibiting the increased levels of SGPT, SGOT, MDA and ALP, as well as showing better histopathological features of liver cells than control [8].

A prior clinical study of the hepatoprotector formula consisting of 6 grams of *Curcuma longa* rhizomes, 28 grams of *Curcuma xanthorrhiza* rhizomes, and 12 grams of *Taraxacum officinale* leaves with a positive control of 2 x 140 mg silymarin was conducted at the traditional medicine clinics in 2015. The results showed that the mean SGPT of subjects taking the hepatoprotector formula decreased from 97.34 IU/L to 39.91 IU/L, which was not significantly different from the mean SGPT of subjects taking silymarin that decreased from 94.63 IU/L to 42.81 IU/L. The mean SGOT of the subjects taking the hepatoprotector formula also decreased from 79.35 IU/L to 36.14 IU/L, which was not significantly different from the mean SGOT of subjects taking silymarin that decreased from 74.55 IU/L to 20.74 IU/L [9].

Considering the higher demands of people who want practicality and for improving their compliance to take herbal medicine, it is necessary to formulate oral preparation that is more practical than infusion water. The drug preparation often used with oral administration is capsule. A study by Mana, et al. in 2017 suggested that the dosage of hepatoprotector herbs in the form of simplicia is equivalent to the form of extract capsule. The determination of effective dosage is calculated based on the yield of water extract. The optimization of capsule formulation using flow-ability, phenol content, flavonoids, total plate count of fungi, as well as stability test, showed that the requirements of extract content is 300 mg/capsule. This extract has used water as a solvent. From these data, a simplicia that consisted of 6 grams of turmeric, 12 grams of dandelion, and 28 grams of curcuma prepared by water infusion is equivalent to 6 extract capsules per day [10].

Nowadays there are still limited variations of drugs with hepatoprotector benefits on the market. One of the most widely used preparations is 7.5 mg of *Fructus schizandrae* (schisandra) fruit extract. The chemical content of schisandra improves liver function by stimulating enzymes in the liver and increasing the growth of liver cells. The common dosage used for this extract is 3 x 2 capsules.

The aim of this study was to obtain scientific evidence about the efficacy and safety of our hepatoprotector *jamu* formula (*Curcuma longa*, *Curcuma xanthorrhiza*, and *Taraxacum officinale* extract) compared to *Fructus schizandrae* extract in mild liver injury.

2. **Material and Methods**

2.1. **Design and site of the study**

This study was a randomized clinical trial using parallel open label design with pre and post test. The trial was conducted by giving our hepatoprotector *jamu* formula to the experimental group and fructus schizandrae extract to the control group. At the first visit, both groups were given 42 capsules and instructed to take 3 x 2 capsules daily (in the morning, afternoon, and evening). Then the patients were
asked to come again to the clinic every week to undergo clinical/laboratory observations and get another capsule for one week supplies. The subjects were asked to take the prescribed medicines for 6 weeks.

This study was conducted between June-November 2018. It took place at Hortus Medicus Clinic, Research and Development Center of Medicinal Plants and Traditional Medicine, Tawangmangu, Central Java, Indonesia. Ethical clearance was approved by the Ethics Commission of National Institute of Health Research and Development, Indonesian Ministry of Health (No: LB 02.01/2/KE 210/2018, dated 31 May 2018).

2.2. Jamu material and preparation
The experimental treatment that we used in this study was hepatoprotector jamu formula in the form of a capsule which is practical to administer and easy to carry. The capsules were prepared by a formulation laboratory in The Research and Development Center of Medicinal Plants and Traditional Medicine. The capsules were made using a dry granulation method of the extract and the additives. The optimal composition of the capsule formula consisted of 300 mg of extract that has used water as a solvent (combination of *Curcuma longa* rhizomes, *Curcuma xanthorrhiza* rhizomes, and *Taraxacum officinale* leaves), 50 mg of aerosil, 50 mg of lactose, 100 mg of Avicel PH102, and 8 mg of stearate. This capsule formulation has met the requirements through the tests for weight uniformity, flow-ability, and disintegration time. Whereas the 7.5 mg of *Fructus schizandrae* fruit extract capsules (commercially marketed as Hp Pro) were used as the control treatment.

2.3. Inclusion and exclusion criteria
The number of participants in this study were 60 subjects (30 were included in the experimental group and 30 subjects were included in the control group). The study subjects had to meet the inclusion criteria as follow: having mild liver injury characterized by an increase of SGOT and SGPT 2-3x upper limit of normal (normal value of SGPT is ≤ 35 IU/L and SGOT is ≤ 40 IU/L), men or women aged 20-50 years, and willing to sign the informed consent. As for the exclusion criteria included subjects who were pregnant or breastfeeding (based on admission), hypersensitive to the ingredients of treatments, having advanced kidney dysfunction, taking drugs that affect the observed conditions, or having complication of severe diseases (such as cirrhosis with massive ascites, hepatoma, jaundice, or bile duct obstruction).

2.4. Outcomes parameter
The efficacy of therapy was performed by examining SGPT and SGOT levels. SGPT is the main laboratory parameter in this study, because SGPT is an enzyme that is mainly produced in the liver. Apart from being produced in the liver, SGOT is also produced in striated muscles, heart muscle, kidney, bone, and brain so that it is less specific to determine liver cell damage [11]. Liver biopsy to determine the degree of liver cells injury was not performed in this study because this examination is invasive so it potentially causes discomfort to the study subjects and has a considerable risk of action.

2.5. Data analysis
Data were analyzed descriptively and using statistical tests (paired t-test). Statistical analysis with IBM SPSS statistics 25.

3. Results and discussion
A total of 60 eligible patients attending RRJ Hortus Medicus participated in this study. 30 were included in the experimental group and 30 subjects were included in the control group. All of the subjects completed the study (figure 1).
Figure 1. Consort diagram.

Demographic and clinical characteristics data includes all eligible subjects (N=60). Most of the subjects were 31-40 years old (57%), men (62%), and civil servant/police/military worker (40%). There were no significant differences in age, sex, and occupation between the experimental group and the control group (p ≥ 0.05). Both groups had similar demographic characteristics (Table 1). The majority of subjects in this study were male (62%) and mostly in the range of 31-40 years (57%). These demographic characteristics were similar to the study in Turkey which showed that most of the patients with NAFLD were in the 3rd and 4th decade (mean age was 38 years) and 76% male[12]. This is also consistent with the study by Guy et al. which showed that men suffered more from NAFLD than women. The estrogen hormone in women was thought to play a role in preventing the development of NAFLD [13]. We used NAFLD as a representative of liver diseases because this type of liver abnormality is quite prevalent among Asian population (around 25%) [14].
Table 1. Demographic characteristics.

| Characteristics            | Hepatoprotector Jamu Formula Group (N = 30) | Fructus Schizandrae Extract Group (N = 30) | Total (N = 60) | p      |
|----------------------------|--------------------------------------------|--------------------------------------------|----------------|--------|
| Age 18-30 years            | 2 (7%)                                     | 4 (13%)                                   | 6 (10%)        | 0.997^a|
| 31-40 years               | 18 (60%)                                   | 16 (53%)                                  | 34             |        |
| 41-50 years               | 6 (20%)                                    | 5 (17%)                                   | 11 (18%)       |        |
| 51-60 years               | 4 (13%)                                    | 5 (17%)                                   | 9 (15%)        |        |
| Sex Male                  | 17 (57%)                                   | 20 (67%)                                  | 37 (62%)       | 0.919^a|
| Female                    | 13 (43%)                                   | 10 (33%)                                  | 23 (38%)       |        |
| Occupation Retired        | 3 (10%)                                    | 5 (17%)                                   | 8 (13%)        | 0.828^a|
| Student                   | 4 (13%)                                    | 3 (10%)                                   | 7 (12%)        |        |
| Civil servant/Police/Military worker | 10 (33%)                                   | 14 (47%)                                  | 24             |        |
| Private officer           | 5 (17%)                                    | 3 (10%)                                   | 8 (13%)        |        |
| Entrepreneur              | 4 (13%)                                    | 2 (7%)                                    | 7 (12%)        |        |
| Laborer/Farmer/Fisherman  | 6 (10%)                                    |                                           |                |        |

^a Chi-square test.

This study found that there was a significant difference of average SGPT levels on day 21 and day 42 compared to day 0 in both hepatoprotector jamu group and Fructus Schizandrae extract group (p< 0.001). The results indicate that these two herbal medicines could significantly reduce SGPT levels since the 21st day. The average SGPT level in the experimental group on day 0 was 83.43 ± 7.90 IU/L, while the average SGPT level in the control group was 87.23 ± 5.71 IU/L. There was no statistically significant difference in SGPT levels on day 0 between two groups (p ≥ 0.05), so the baseline was equal. SGPT levels between the experimental group and the control group were also not statistically different on day 21 and day 42 (p ≥ 0.05). It means that the effectiveness of the hepatoprotector jamu formula was equivalent to the Fructus schizandrae extract in reducing SGPT levels (Table 2).
Table 2. Comparison of SGPT levels in each group.

| Time of Measurement | hepatoprotector jamu group | Fructus schizandraceae extract group |
|---------------------|-----------------------------|-------------------------------------|
|                     | Mean ± SD (IU/L) | p value (compared to baseline) | Mean ± SD (IU/L) | p value (compared to baseline) |
| Day 0 (Baseline)   | 83.43 ± 7.90       | -                                | 89.03 ± 7.42     | -                                |
| Day 21             | 51.87 ± 11.80      | <0.001<sup>b</sup>               | 54.47 ± 12.89    | <0.001<sup>b</sup>               |
| Day 42             | 35.03 ± 7.79       | <0.001<sup>b</sup>               | 41.43 ± 7.42     | <0.001<sup>b</sup>               |

<sup>b</sup> = Paired t-test.

SGOT is an additional laboratory parameter in assessing liver function. However, SGOT is not specifically produced in the liver but also in striated muscle cells. An increase in SGOT ≥ 2x upper limit of normal along with an increase in SGPT indicates impaired liver function. Compared to the baseline, there were a significant difference of average SGOT levels on the follow up days in hepatoprotector jamu group (p = 0.023 on day 21; p = 0.003 on day 42) as well as Fructus Schizandrae extract group (p = 0.028 on day 21; p = 0.042 on day 42). The results suggest that both herbal medicines could significantly reduce SGOT levels since the 21<sup>st</sup> day. The average SGOT level in the hepatoprotector jamu formula group on day 0 was 81.43 ± 9.30 IU/L, while in the Fructus Schizandrae extract group was 87.93 ± 5.9 IU/L (Table 3).

Table 3. Comparison of SGOT levels in each groups.

| Time of Measurement | hepatoprotector jamu group | Fructus schizandraceae extract group |
|---------------------|-----------------------------|-------------------------------------|
|                     | Mean ± SD (IU/L) | p value (compared to baseline) | Mean ± SD (IU/L) | p value (compared to baseline) |
| Day 0 (Baseline)   | 81.43 ± 9.33       | -                                | 87.93 ± 5.93     | -                                |
| Day 21             | 51.83 ± 11.06      | 0.023<sup>b</sup>               | 54.77 ± 11.07    | 0.028<sup>b</sup>               |
| Day 42             | 29.27 ± 7.33       | 0.003<sup>b</sup>               | 35.79 ± 8.90     | 0.042<sup>b</sup>               |

<sup>b</sup> = Paired t-test

The baseline was equal because there was no statistically significant difference in SGOT levels on day 0 between two groups (p ≥ 0.05). This study found that the average SGOT levels between the experimental group and the control group was not statistically different on days 21 and day 42 (p ≥ 0.05). It means the effectiveness of the jamu formula group was equivalent to the Hp Pro group in reducing SGOT levels.

This study found that there was a significant reduction of average SGPT and SGOT levels on day 21 and day 42 compared to day 0 in the hepatoprotector jamu group (p < 0.05). These results showed that the experimental treatment might significantly improve liver damage in the subjects. The hepatoprotective activity of this herbal extract was obtained from active compounds of the three plants (*Curcuma xanthorrhiza*, *Curcuma longa*, *Taraxacum officinale*) which work synergistically to protect and improve liver function.
Table 4. Comparison of SGOT and SGPT levels between the hepatoprotector jamu formula group and the Fructus schizandae extract group.

| Time of Measurement | SGPT p value | SGOT p value |
|---------------------|--------------|--------------|
| Day 0 (Baseline)    | 0.774<sup>c</sup> | 0.211<sup>c</sup> |
| Day 21              | 0.661<sup>c</sup> | 0.424<sup>c</sup> |
| Day 42              | 0.420<sup>c</sup> | 0.350<sup>c</sup> |

<sup>c</sup> = Independent t-test

Curcuma xanthorrhiza (javanese turmeric) has been used in traditional medicine for a long time to treat liver diseases. Previous animal studies showed that the extract of Curcuma xanthorrhiza could significantly reduce the elevation of SGPT and SGOT levels in rats with liver damages induced by alcohol, carbon tetrachloride, or paracetamol [9,10]. The possibility of hepatoprotective mechanism of Curcuma xanthorrhiza may be due to its antioxidant properties, either by scavenging free radicals or by reducing oxidized compounds. Excessive free radicals, such as reactive oxygen species (ROS), become toxic hazards to various biological molecules through lipid peroxidation, DNA damage, and inhibition of protein synthesis. Those damages result in many degenerative diseases, including liver injury. Since free radicals play an important role in hepatotoxicity, plant antioxidants become promising hepatoprotector agents against liver lesions. The major compound in Curcuma xanthorrhiza which is found to have antioxidant and hepatoprotective activity is xanthorrhizol[15]. A study using standardized xanthorrhizol extract given to rats with ethanol pretreatment was found to reduce SGPT, SGOT, SGPT and serum protein, and improve the histopathology of liver tissue [13]. Other study on mice with acute liver damage induced by intraperitoneal paracetamol and carbon tetrachloride also showed that Curcuma xanthorrhiza extract could reduce the elevation of serum transaminase levels significantly and alleviated the degree of liver damage at 24 hours after the administration of those two hepatotoxins [16].

Curcuma longa (turmeric) contains curcumin as the main active compound which has hepatoprotective activity. The mechanism of hepatoprotective action of curcumin has been investigated through inhibition of the inflammatory cytokines (including interferon-γ, TNF-α, interleukin-6), reducing lipid peroxidation products, activation of hepatic stellate cells (HSC), and improving cellular response to oxidative stress. Previous studies found that curcumin supplementation could improve several liver diseases, including hepatitis, NAFLD, cirrhosis, and liver cancer (HCC). Curcumin can be used as an alternative treatment for patients with chronic hepatitis. It exhibits antioxidant properties by scavenging and breaking the chains of superoxide ions to prevent liver damage. It also increases glutathione S-transferase, acts as anti-inflammation, and inhibits the replication of hepatitis B virus [17]. A randomized clinical trial on 50 patients with NAFLD suggested that lifestyle modification advice plus curcumin supplementation for 12 weeks was associated with statistically significant decrease in serum level of liver enzymes, hepatic steatosis, TNF-α, hepatic fibrosis, and nuclear factor-kappa B activity compared to baseline [18]. In the rat model using magnetic resonance-based electrical conductivity imaging method, cirrhotic liver tissues induced by dimethyl nitrosamine (DMN) that were treated with curcumin showed increased conductivity than tissues in DMN-only group. Moreover, the conductivity of cirrhotic liver after curcumin treatment was similar to normal liver tissues. Immunohistochemical and biochemical examination also showed significant levels of attenuated fibrosis, decreased inflammatory response, as well as lower SGPT and SGPT in DMN+curcumin group than DMN-only group. In liver cancer studies, curcumin remains a promising therapeutic agent for HCC treatment. The evidence from in vitro and in vivo models showed that curcumin held a good prognosis as a curative agent for HCC. However, further research is still needed to determine sufficient dosage to enhance its bioavailability and investigate its anticancer effects in clinical studies [19].
Taraxacum officinale (dandelion) is a medicinal plant that has been traditionally used as hepatoprotector. Current pharmacological studies found that Taraxacum officinale extract has hepatoprotective properties due to antioxidant and anti-inflammatory activities as well as reducing lipid accumulation in the liver. This plant contains chicoric acid that inhibits cell penetration by virus and prevents collagen oxidation as well as chlorogenic acid that promotes the flow of bile [20]. A prior animal study revealed that dandelion leaf water extract could perform significant protection against carbon tetrachloride induced cirrhosis in albino rats. The blood samples from dandelion treated animals showed significant reduction in serum markers for liver injury, indicating the effect of this extract in restoring functional ability of hepatocytes [21]. Other animal studies also found that Taraxacum officinale extract could reduce oxidative liver damage in Wistar rats with sodium dichromate induced hepatotoxicity [20].

4. Conclusion
There was a significant difference of average SGPT dan SGOT levels on day 21 and day 42 compared to day 0 in both hepatoprotector jamu group and Fructus Schizandrae extract group. The administration of hepatoprotector jamu formula (combination of Curcuma longa, Curcuma xanthorrhiza, and Taraxacum officinale extract) was equivalent to fructus schizandrae extract for lowering SGPT and SGOT levels in subjects with mild liver injury.

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