

Role of Phytopharmacy as Hepatoprotector in Chronic Hepatitis

Budi Herlianto*, Syifa Mustika**, Supriono**, Bogi Pratomo**, Harijono Achmad**

* Department of Internal Medicine, Faculty of Medicine, University of Brawijaya/
Dr. Saiful Anwar General Hospital, Malang

** Division of Gastroentero-hepatology, Department of Internal Medicine,
Faculty of Medicine, University of Brawijaya/Dr. Saiful Anwar General Hospital, Malang

ABSTRACT

Background: Hepatitis is one of the health problems in Indonesia that require special treatment, in line with the increase of morbidity and mortality rate of this disease. Complications of hepatitis include liver cirrhosis and hepatocellular carcinoma. Indonesia, as a tropical country, has many medicinal plants that act as hepatoprotector, a substance that can protect liver from toxic agent. Use of medicinal plants is still considered as controversial treatment because there is still lack of studies. Medicinal plants with mix composition of phytopharmacy, such as: *Curcuma xanthorrhiza*, *Arcangelesia flava*, *Nigella sativa*, and *Kleinhovia hospita* show potency as hepatoprotector. The objective of this study is to analyse the function of phytopharmacy as hepatoprotector in chronic hepatitis.

Method: This study is a clinical trial performed in the Gastroenterology Department and Outpatient Clinic in Saiful Anwar Hospital in May-June 2013. Chronic hepatitis B or C patients who have received antiviral therapy with > 3 fold increase of the threshold value of transaminase level, were included in this study. In this study, patients consumed phytopharmacy tablet 3 times per day. After 7 days of treatment, patients' serum transaminase levels (ALT and AST) were re-assessed. Statistical analysis of before and after treatment data was performed using Wilcoxon test and the result was significant with $p < 0.05$.

Results: From 10 patients, the average age was 50.3 years old. Sixty percent (60%) of them were male, with 50% suffered from chronic hepatitis B and the other 50% suffered from chronic hepatitis C. From this study, decrement of alanine transaminase (ALT) and aspartate transaminase (AST) after seven days of treatment were 45.06%, with $p = 0.007$ and 48.63%, with $p = 0.007$, respectively

Conclusion: Phytopharmacy supplementation in chronic hepatitis can decrease serum transaminase, however further study is needed.

Keywords: chronic hepatitis, phytopharmacy, ALT, AST, hepatoprotector

ABSTRAK

Latar belakang: Hepatitis merupakan salah satu masalah kesehatan di Indonesia yang memerlukan penanganan khusus, seiring dengan meningkatnya angka morbiditas dan mortalitas penyakit ini. Komplikasi dari hepatitis meliputi sirosis hepatitis dan karsinoma hepatoseluler. Indonesia sebagai negara tropis memiliki banyak tanaman obat dengan hepatoprotektor sebagai zat yang dapat melindungi hati dari agentoksik. Penggunaan tanaman obat masih dianggap sebagai pengobatan yang kontroversial karena belum terdapat penelitian yang cukup. Tanaman obat dengan bahan campuran fitofarmasi seperti temulawak, *Arcangelesia flava*, *Nigella sativa*, dan *Kleinhovia hospita* yang menunjukkan potensi sebagai hepatoprotektor. Tujuan dari penelitian ini adalah untuk menganalisis fungsi fitofarmasi sebagai hepatoprotektor pada hepatitis kronis.

Metode: Penelitian ini merupakan uji klinis yang dilakukan di Departemen Gastroenterologi dan ruang rawat jalan di Rumah Sakit Saiful Anwar pada bulan Mei-Juni 2013. Pasien hepatitis B atau C kronis, dan telah mendapat terapi antivirus dengan peningkatan transaminase > 3 kali nilai batas atas dimasukkan dalam penelitian ini. Dalam penelitian ini, pasien mengonsumsi tablet 3dd1 fitofarmasi setelah 7 hari, serum transaminase pasien (ALT dan AST) diukur. Analisis statistik dilakukan sebelum dan setelah tes Wilcoxon, dan hasilnya signifikan $p < 0,05$.

Hasil: Dari 10 orang pasien, didapatkan rerata umur adalah 50,3 tahun. Enam puluh persen (60%) adalah laki-laki, dengan 50% hepatitis B kronis, dan 50% hepatitis C kronis. Dari penelitian ini, didapatkan decrement dari alanine transaminase (ALT) adalah 45,06%, dengan $p = 0,007$ dan aspartate transaminase (AST) adalah 48,63% dengan $p = 0,007$ setelah 7 hari penanganan.

Simpulan: Suplementasi Fitofarmasi pada hepatitis kronis dapat menurunkan serum transaminasi, namun diperlukan penelitian lebih lanjut.

Kata kunci: hepatitis kronis, fitofarmasi, ALT, AST, hepatoprotektor

INTRODUCTION

Liver disease is one of the main causes of morbidity and mortality in human regardless of age. According to World Health Organization (WHO), it is estimated that globally 170 million patients are infected with hepatitis C and they do not realise it. More than 2 million people are infected with hepatitis B and more than 5 million people are infected with acute hepatitis B. Therefore, this chronic liver disease has great impact to human world wide.¹ Liver is the largest organ in human's body which has many functions related to one another. Several causes of liver abnormalities that have been known include viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver, autoimmune liver disease, drug-induced liver injury, and others. Acute hepatitis is initially asymptomatic, and may resolve by itself without the presence of sequelae. However, inflammation which progresses and occurs more than 6 months will cause chronic condition. Consequences of chronic hepatitis include the emergence of portal hypertension and liver cirrhosis.¹ Inflammatory markers in liver cells are increased level of the serum transaminases. These serum transaminases include aspartate transaminase (AST) and alanine transaminase (ALT). Both of these serum transaminases will increase in liver cells injury. The more liver cells are injured, the more severe is the degree of liver injury.²

Hepatoprotector is defined as drugs that protect liver from the detrimental effect from endogenous or even exogenous factors by decreasing effect of inflammation and decreasing disease progression. The presence of this hepatoprotector is still debatable.³ Medicinal plants have been widely known and used as hepatoprotective agent. The use of this herbal-derived medicine is quite common, as much as 80% of the world population,

mostly used by developing countries. This is because herbal medicines economically cheaper because it is obtained from easily renewable resources. Many ancient literatures stated that this medicine is used in diseases with no modern drugs to treat or as a palliative therapy. Additionally, people in the society believe on its safety, efficacy, and minimal side effects after long-term treatment, based on tradition.⁴

Phytopharmacy which is used in this study is a phytomedicine which acts as hepatoprotector and is an extract mix of 75 mg *Curcuma xanthorrhiza*, 50 mg *Arcangelesia flava* 50 mg, 100 mg *Nigella sativa*, 100 mg *Kleinhovia hospital* and 100 mg *Ophiocephalus striatus*. This phytomedicine is a combination of several medicinal plants that function as hepatoprotector. In this study, we would like to identify the role of phytopharmacy as hepatoprotector in chronic hepatitis.

METHOD

This study was a pre and post-treatment clinical trial to 10 chronic hepatitis patients (chronic hepatitis B and chronic hepatitis C), with positive results of HbsAg or anti-HCV, increased serum transaminase levels (AST or ALT) more than 3 times upper normal limit (8-40 IU). Chronic hepatitis B or C patients who have received antiviral therapy with > 3 fold increase of the threshold value of transaminase level, were included in this study. The study was done from May to June 2013 and patients were recruited from Gastroenterology Outpatient Clinic and Inpatient Ward in Saiful Anwar Hospital. Afterwards, patients' serum transaminases were evaluated before and after 7 days of treatment. Patients were asked to consume phytopharmacy 1 capsule 3 times daily for 7 days. After

7 days of treatment, patients' serum transaminase levels (ALT and AST) were re-assessed. Statistical analysis of before and after treatment data was performed using Wilcoxon test and the result was significant with $p < 0.05$.

RESULTS

Average age of these patients was $50.30 \pm 9,429$ years old (SD). All patients have received antiviral therapy. All of them also have given their consent before included in this study. All data pre or post treatment was analysed using Wilcoxon test, because the data obtained from this study were nonparametric data.

Table 1. Basic data of hepatitis patients

Variable	n (%)
Age (average)	50.3 9.429
Sex	
Male	6 (60%)
Female	4 (40%)
Hepatitis	
B	5 (50%)
C	5 (50%)
AST (average)	403 ± 415
ALT (average)	294.9 ± 284

AST: aspartate transaminase; ALT: alanine transaminase

The average AST after 7 days of treatment was 200.3 ± 216.6 . The average ALT 7 days after treatment was 151.1 ± 155.35 . AST changes after 7 days of treatment was 45.06%. Decreased ALT after 7 days of treatment was 48.63%. Using Wilcoxon test, it was obtained that the results were significant with $p < 0.05$.

Table 2. Results after 7 days of treatment

Serum	Treatment	Decreased (%)	p
AST	200.3 ± 216.6	45.06	0.07
ALT	151.1 ± 155.35	48.63	0.07

AST: aspartate transaminase; ALT: alanine transaminase

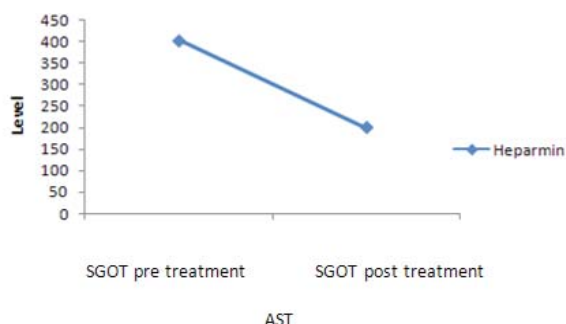


Figure 1. Graph showing average of AST pre and post-treatment

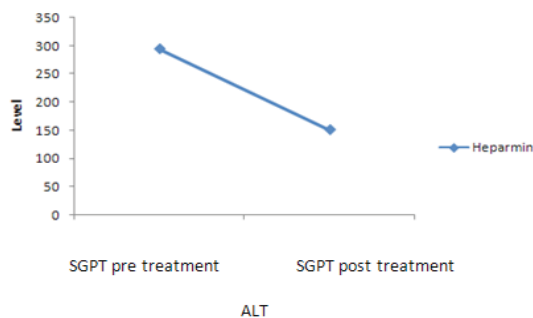


Figure 2. Graph showing average of ALT pre and post-treatment

DISCUSSION

In this study, we evaluated the administration of phytopharmacy as hepatoprotector in chronic hepatitis patients who suffer from liver injury, marked by the presence of increased serum transaminase more than 3 times normal. Increased of serum transaminase showed the presence of injury to the liver cells; the higher the transaminase level, the larger the number of injured liver cells. Liver cells injury due to hepatitis might result from the direct effect of the virus or even from the effect of inflammatory cells attacking cells that have been infected by hepatitis virus. In hepatitis B, hepatocytes that have been infected by hepatitis B virus will be eliminated by CD8 T cells; likewise in hepatitis C infection, immune cells also influence the hepatocyte injury. However, in hepatitis C, it was also thought that hepatitis C virus also has the ability to destruct liver cells.⁵ Generally, the use of hepatoprotector is still controversial.⁶ Overall, hepatoprotector acts in several mechanisms, such as stabilization from cell membrane and organelles, antioxidant effect, detoxification effect, anti-inflammatory effect, stimulation of liver cells regeneration, and immunomodulation effect. Hepatoprotector classification is from herbal preparation, from amino acid, bile acid derivation, from vitamins and antioxidants and other substances.

In this study, we use phytopharmacy, which is a combination of 5 types of herbal substances. These five herbal substances act as hepatoprotector by using effect from antioxidants and cell membrane and organelles stabilization. *Curcuma xanthorriza* is believed by the people in the community as hepatoprotector. Administration of the extract of this substance may prevent liver injury due to inflammatory process. The other active substance is curcuminoid. Curcuminoid has antioxidant and anti-inflammatory characteristics.⁷ *Arcangelesia flava* is a wild plant usually grows in the rocky beach. The active substance of *Arcangelesia flava* is berberine. Berberine has potency as effective antioxidant.⁸

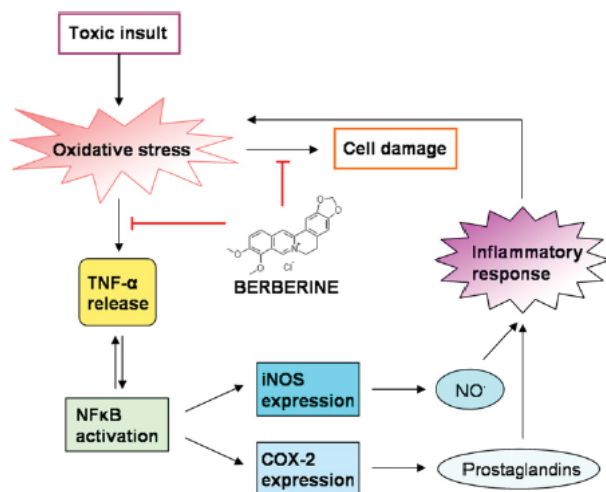


Figure 3. Antioxidant mechanism of Berberine. Berberine inhibits the release of TNF- α , and prevents direct injury caused by oxidative stress, marked by decreased level of lipid peroxidase (oxidative stress marker).⁸

Nigella sativa L has been widely studied in Middle East countries; the active substance is Thymoquinone. This thymoquinone acts as quite potent antioxidants. In a study, administration of thymoquinone has hepatoprotective effect towards mouse's liver which was injured by CCl₄.⁹ The active substance contained in *Kleinhovia hospita* is Cycloartane triterpenoids. This substance has revealed its hepatoprotective effect in human liver cells that are injured by nitrofurantoin.¹⁰ The mechanism of this substance is by anti-oxidant effect.^{11,12} The last compound of this phytopharmacy is *Opiocephalus striatus*. The extract of this snakehead murrel may help to increase serum albumin in human.¹³

In this study, there was decreased level of AST as much as 45.06% and ALT as much as 48.63%. Hepatoprotective mechanism of heparmine is as antioxidant and anti-inflammatory. This anti-inflammatory effect will decrease serum transaminase by decreasing permeability of cell wall, particularly hepatocytes, as a result of inflammation. This decrease is statistically significant. There are many limitations in our study, including very small sample size and different initial transaminase level between samples.

Conclusion

From this study, we concluded that administration of phytopharmacy might decrease serum transaminase in chronic hepatitis patients, with significantly statistic results. However, there are many limitations in this study.

REFERENCES

1. Negi, Kumar JK, Lugman S, Shanker K, Gupta MM, Khanuja SP. Recent advances in plant hepatoprotectives: a chemical and biological profile of some important leads. *Med Res Rev* 2008;28:767-72.
2. Giboney PT. Mildly elevated liver transaminase levels in the asymptomatic patient. *Am Fam Physician* 2005;71:1105-10.
3. Sulaiman HA, Sulaiman AS. Obat herbal pada penyakit hati. *Buku Ajar Ilmu Penyakit Hati*. 1sted. Jakarta: Sagung Seto, 2012.p.639-45.
4. Kashaw V, Nema AK, Agarwal A. Hepatoprotective prospective of herbal drugs and their vesicular carriers – a review. *Int J Res Pharm Biomed Sci* 2011;2:360-74.
5. Sanityoso A. Hepatitis viral akut. Sudoyo AW, Setiyohadi B, Simadibrata M, Setiati S, eds. *Buku Ajar Ilmu Penyakit Dalam*. Jakarta: Intern Pub 2009.p.644-52.
6. Feng-min L, Hui Z. Management of hepatitis B in China. *Chin Med J* 2009;122:3-4.
7. Devaraj S, Ismail S, Ramanathan S, Marimuthu S, Fei YM. Evaluation of hepatoprotective activity of standardized ethanolic extract of *Curcuma xanthorrhiza* Roxb. *J Med Plants Res* 2010;4:2512-7.
8. Dominotrix R, Jakovac H, Blagojevic G. Hepatoprotective activity of berberine is mediated by inhibition of TNF- α , COX-2, and iNOS expression in CCl₄-intoxicated mice. *Toxicology* 2011;280:33-43.
9. El-Tawil OS, Moussa SZ. Antioxidant and hepatoprotective effects of thymoquinone against carbon tetrachloride-induced hepatotoxicity in isolated hepatocytes. *J Egypt Soc Toxicol* 2006;34:33-41.
10. Gan LS, Ren G, Mo JX, Zhang XY, Yao W, Zhou CX. Cycloartane triterpenoids from *Kleinhovia hospita*. *J Nat Prod* 2009;72:1102-5.
11. ET Arung, Kusuma IW, Purwatiningsih S, Roh SS, Yang CH, Jeon S, et al. Antioxidant activity and cytotoxicity of the traditional Indonesian medicine Tahongai (*Kleinhovia hospita L.*) extract. *J Acupunct Meridian Stud* 2009;2:306-8.
12. Zhou CX, Zou L, Gan LS, Cao YL. Kleinhosptines A-D, new cycloartane triterpenoid alkaloids from *Kleinhovia hospita*. *Org Lett* 2013;15:2734-7.
13. Mustafa A. Albumine and zinc content of Snakehead fish. *IEESE Int J Sci Tech* 2012;1:1-8.

Correspondence:
 Harijono Achmad
 Division of Gastroentero-hepatology
 Department of Internal Medicine
 Dr. Saiful Anwar Hospital
 Jl. Jaks Agung Suprpto No.2 Malang Indonesia
 Phone/facsimile: +62-341-348265
 E-mail: harijono_achmad@yahoo.com