International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 9, Issue 5, 2017

Original Article

HEPATOPROTECTIVE ACTIVITY COMBINATION OF *CURANGA FEL-TERRAE* LOUR LEAVES AND *CURCUMA HEYNEANA* VALETON AND ZIJP RHIZOME IN RAT INDUCED BY COMBINATION OF RIFAMPIN AND ISONIAZID

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Received: 09 Dec 2016 Revised and Accepted: 09 Mar 2017

ABSTRACT

Objective: The liver is a vital organ in the body, it is often exposured to the xenobiotics that can cause injury. Pugun tano (*Curanga fel-terrae*) and temu giring (*Curcuma heyneana*) are plants that have been claimed to cure many ailments including protecting the liver. But the hepatoprotective properties of the combination of these plants has not been well studied. In this regard, the current study was undertaken to evaluate the activity combination of those plants.

Methods: The male Wistar rats were divided into 6 groups, group I was a negative control (CMC-Na); group II-IV were the treatment groups and were given combination extracts at the doses of 50 mg/kg, 75 mg/kg and 100 mg/kg respectively; group V was positive control (catechin) and group VI was normal control. All of groups except group VI were given combination rifampin 100 mg/kg and isoniazid 50 mg/kg for 15 d along with administration of extracts. At the day 16, rats were sacrificed. Histopathology of the liver and biochemical assay of blood was done at the end of the administration.

Results: The administration of the combination of *C. fel-terrae* and *C. heyneana* at the doses of 75 and 100 mg/kg significantly inhibited the elevation of aspartate aminotransferase (AST) and alanine transaminase (ALT) compared to negative control ($p<0.05$). Histopathological assessment of the liver was comparable to the normal control ($p>0.05$).

Conclusion: The combination of *C. fel-terrae* and *C. heyneana* at the dose of 75 and 100 mg/kg is able to protect the liver from damage induced by rifampin and isoniazid.

Keywords: *Curanga fel-terrae*, *Curcuma heyneana*, Hepatoprotective, Rifampin, Isoniazid

DOI: http://dx.doi.org/10.22159/ijpps.2017v9i5.16528

INTRODUCTION

Drug-induced liver injury (DILI) is serious problem commonly associated with using of particular drugs like those used in the treatment of tuberculosis [1]. This situation can limit the use of antituberculosis drugs and can cause the failure of therapy. Hence, newer strategies must be found to address the problem in order to enhance the compliance of tuberculosis patients [2].

C. heyneana is known as temu giring or kuning gajah. It is an annual plant that has been used as a material of traditional medicine (jamu) in Indonesia, Malaysia and even in China for traditional Chinese Medicine (TCM). It has efficacy as anthelmintic because it contains citric piperazine which is able to tackle *Ascaris* [3]. This plant is abushes, height about 1 until 2 m, has rhizome and from Zingiberaceae tribe [4]. Genus curcuma contains the sort of chemical constituents and has broad bioactivities such as anti-oxidants, antitumor and anti-inflammatory as well as antimicrobial [5-6]. Constituents from *C. heyneana*are curcumenol, isocurcumenol, along with phytosterols, stigmasterol and alpha-sitosterol showed moderate inhibition against CEM-SS in cytotoxic assay [6]. It is also inhibited protein tyrosine phosphatase 1B (PTP1B) which is considered to be involved in the etiology of diabetes mellitus, neural diseases regulation of allergy and inflammation or they are even considered to be responsible for the pathogens [7-8].

C. fel-terrae or pugun tano is a smooth, prostrate herb. It is also known as *Picria fel-terrae*. Its common names is sagai-uak or curanja. It has been used traditionally in Karo district, North Sumatera, Indonesia, stimulant and treat diabetes mellitus as well as malaria. Previous reports said that it has pharmacological activities such as a diuretic, cardioprotective, induced apoptosis, cell cycle arrest and suppressing cyclin D1 and Bcl-2 expression, antidiabetic and inhibitory effect to acetylcholine muscarinic-3 receptors which is related as anti-asthma [9-13].

Previous research has reported that the ethanolic extract of *C. fel-terrae* leaves at the dose of 125 mg/kg can protect the liver from the damage caused by high doses of paracetamol [14]. Other authors have also mentioned that ethanolic extract of *C. heyneana* rhizome at the dose of 125 mg/kg can protect the liver against injury caused by high doses paracetamol as well as the combination of anti-tuberculosis drugs rifampin and isoniazid [15-16]. The activity was comparable to catechin which has been recommended as hepatoprotective agent [17]. Based on the potency of these plants, this study is aimed at exploring the combination of both extracts to establish an effective dose and possible synergistic effect from the extracts in protecting against liver damage induced by the antituberculosis drugs rifampin and isoniazid. The long-term aim was to formulate this extracts into a phytopharmaceutical agent for possible use along with the conventional antituberculosis drugs to prevent the associated liver damage.

Fig. 1: Picture of the plants, (A) rhizome of *C. heyneana*; (B) leaves of *C. fel-terrae*

MATERIALS AND METHODS

Plant material and extraction

C. fel-terrae and *C. heyneana* were collected from Pancur Batu subdistrict, Deli Serdang district. Collected plant samples were washed under running tap water, dried, powdered in a grinder and stored in airtight jars. The plant identification was confirmed by The Indonesian Academy of Sciences, Indonesia Number 1775/IPH.1.01/ If.07/ VIII/2016. As much as 220 gram the dried leaves of *C. fel-terrae* and 212 gram rhizome of *C. heyneana* were extracted with maceration method using 2.5 L of ethanol until discoloration, then ethanol was evaporated at 40 °C in a rotary vacuum evaporator. The yield of *C. fel-terrace* leaves extract was 26.55 gram (12.07%) and for *C. heyneana* was 25.48 gram (12.02%). The extracts were stored at 2-8 °C and used for determining the activity. The percentage yield of extracts was calculated by the following formula:

$$\text{Yield \%} = \frac{\text{weight of dry crude extract obtained (g)}}{\text{weight of plant material before extraction (g)}} \text{ x100}$$

Chemicals and reagents

Rifampin (Sandoz, Indonesia), isoniazid (Sandoz, Indonesia), ethanol (Merck, Germany), sodium carboxymethyl cellulose (CMC-Na) (Sigma-Aldrich), catechin (Sigma-Aldrich), reagent kit alanine aminotransferase (ALT) (DiaSys®), reagen kit aspartate amino-transferase (AST) (DiaSys®), neutral buffered formalin 10%, and hematoxylin and eosin stain. All biochemical measurements were performed using UV-Vis spectrophotometer (*Thermo scientific).*

Animals

All treatments to the animal and procedure were evaluated by Ethic Committee Faculty of Medicine, University of Sumatera Utara No. 653/TGL/KEPK FK USU-RSUP HAM/2016. Thirty male Wistar rats (180±20 g) were obtained from Animal Breeding Unit, Faculty of Pharmacy, University of Sumatera Utara. The animals were kept under standard laboratory conditions and allowed a natural light-dark cycle. The rats were fed on a standard pellet diet and provided access to water *ad libitum*.

Hepatoprotective activity

After 7 d of acclimatisation, animals were divided into six groups of five rats. Liver damage was induced by the administration of isoniazid 50 mg/kg and rifampin 100 g/kg [18]. Every day the rats were given combination extracts of *C. fel-terrae* and *C. heyneana* as well as isoniazid and rifampin as long as 15 d. On the 16th day, all rats were sacrificed by mild ether anesthesia. The blood and the liver were withdrawn in order to be determined the activity of ALT and AST enzymes, microscopic and macroscopic of the liver (Table 1).

Table 1: Experimental design of hepatoprotective activity from combination of *C. fel-terrae* and *C. heyneana*

Group	Treatment
I: (negative control)	CMC–Na 0,5%+isoniazid 50 mg/kg+rifampin 100 mg/kg
II: (dose of 50 mg/kg)	EECF 50 mg/kg+EECH 50 mg/kg+isoniazid 50 mg/kg+rifampin 100 mg/kg
III: (dose of 75 mg/kg)	EECF 75 mg/kg+EECH 75 mg/kg+isoniazid 50 mg/kg+rifampin 100 mg/kg
IV: (dose of 100 mg/kg)	EECF 100 mg/kg+EECH 100 mg/kg+isoniazid 50 mg/kg+rifampin 100 mg/kg
V: (positive control)	catechin 2 mg/kg+isoniazid 50 mg/kg+rifampin 100 mg/kg
VI: (normal control)	Without treatment

EECF=ethanolic extract of *C. fel-terrae*; EECH=ethanolic extract of *C. Heyneana*

Analysis of liver enzymes

The blood sample was collected from the vein of the heart of each animal. Serum was separated and stored at 2-8 °C before it was used to determine the activity of AST and ALT. The liver was taken for histopathological analysis.

Macroscopic assessment of the liver

Liver obtained from the rats were washed with NaCl 0.9%. The observation was done toward the intensity of colour, texture of liver surface as well as organ weight in order to calculate the liver relative index.

$$\text{Liver relative index (\%)} = \frac{\text{weight of liver (g)}}{\text{final body weight (g)}} \text{ x 100}$$

Microscopic of the liver

The liver tissue was treated with 10%(v/v) formalin buffer and then embedded in paraffin. Slicing was done using a microtome and stained with haematoxylin and eosin and observed by using a microscope.

Statistical analysis

Results were expressed as Means±Standard error (SE). Statistical analysis were carried out using one-way analysis of variance followed by a Tukey *post-hoc* test (SPSS Version 18; SPSS Inc., Chicago, IL, USA). Statistical significance was set at P<0.05. The *p*-values are presented with obtained data.

RESULTS

Macropathology liver organ

Table 2 and fig. 2 revealed the macromorphological study which has been done on the liver. The liver of negative control has white spot. Unlike negative control, the other groups have no white spot in the liver. It means that there is protection from the extracts to the liver. The colour of negative control and a dose of 50 mg/kg is pale red, whereas the others red to reddish-brown.

Table 2: Macropathology of liver organ and liver relative index from rats. Data were presented as mean±SEM (n=5)

Group	Parameter of observation		Liver relative index mean±SEM
	Colour	Texture	
Negative control	Pale red	Smooth with some white spots	4.61±0.16
Dose of 50 mg/kg	Red	Smooth	4.51±0.20
Dose of 75 mg/kg	Reddish-brown	Smooth	3.14±0.11^{abc}
Doseof 100 mg/kg	Reddish-brown	Smooth	3.61±0.04^{abc}
Positive control	Reddish-brown	Smooth	3.35±0.17^{ab}
Normal control	Reddish-brown	Smooth	3.09±0.06^{ac}

significantly different wit negative control group (p<0.05), same as a normal control group, ^{c}same as positive control group (p>0.05)

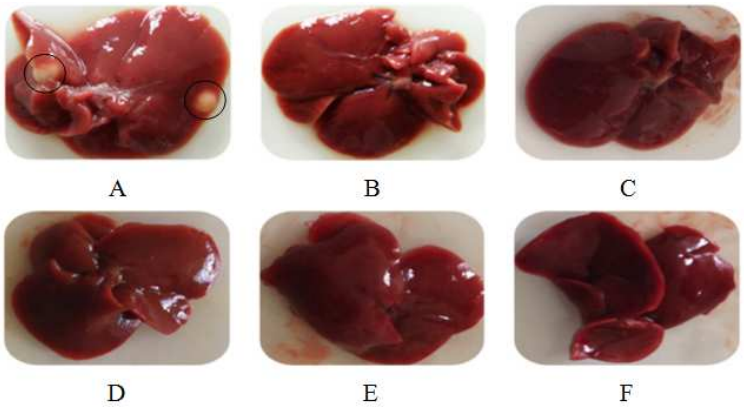


Fig. 2: Macroscopic of the liver, (A) negative control, the liver with white spot and the colour is pale red; (B) dose of 50 mg/kg, the liver has no spot and the colour is pale red; (C) dose of 75 mg/kg, the liver has no spot and the colour is reddish brown; (D) dose of 100 mg/kg, the liver has no spot and the colour is reddish brown; (E) positive control, the liver has no spot and the colour is reddish brown; (F) normal control, the liver has no spot and the colour is reddish brown

Organ-to-body weight ratio shows that injury causes the weight of the liver is increase significantly compared to the normal control group ($p<0.05$). However, the weight of the liver from groups at the doses of 75 and 100 mg/kg did not increase. Therefore administration of extracts is able to prevent the injury in the liver.

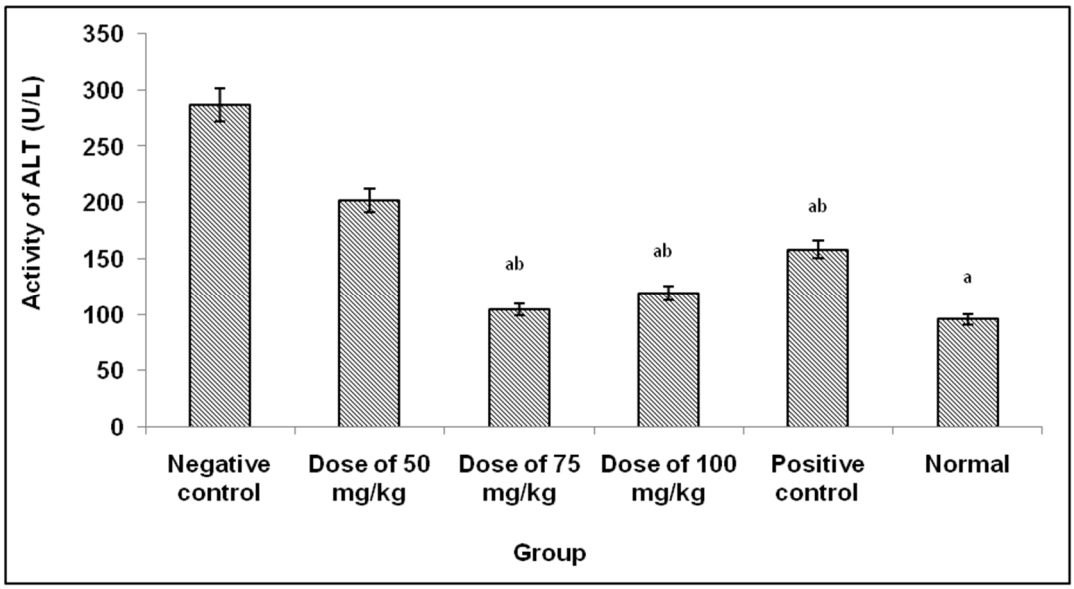
Biochemical determination

Based on table 3 and fig. 3, ALT of the negative control group increased significantly due to induction of rifampin and isoniazid compared to normal group ($p<0.05$). Administration combination of extracts at the dose of 50 mg/kg could not prevent elevation of ALT. Whereas at the doses of 75 and 100 mg/kg, the combination of extracts was able to prevent increasing of ALT compared to negative control group ($p<0.05$). Moreover, the ALT value of those groups was the same as normal control. It means that groups at the doses of 75 and 100 mg/kg had hepatoprotective activity. Besides ALT, AST increased significantly compared to normal group ($p<0.05$). Administration combination of extracts at the dose of 50 mg/kg could not prevent elevation of AST. Whereas at the doses of 75 and 100 mg/kg, the combination of extracts was able to prevent the elevation of AST compared to negative control group ($p<0.05$).

Table 3: Hepatoprotective activity from combination of extracts toward biochemical parameter. Data were presented as mean±SEM (n=5)

Group	ALT (U/l) mean±SEM	AST (U/l) mean±SEM
Negative control	287.00±58.89	251.00±32.91
Dose of 50 mg/kg	202.00±6.93	210.50±12.99
Doseof 75 mg/kg	104.50±10.10[ab]	141.00±1.15[a]
Doseof 100 mg/kg	119.00±2.31[ab]	161.00±15.01[a]
Positive control	158.50±2.02[ab]	146.00±5.77[a]
Normal control	96.00±6.35[a]	41.00±2.65[a]

[a]significantly different with the negative control group ($p<0.05$), [b]same as a normal control group ($p>0.05$)



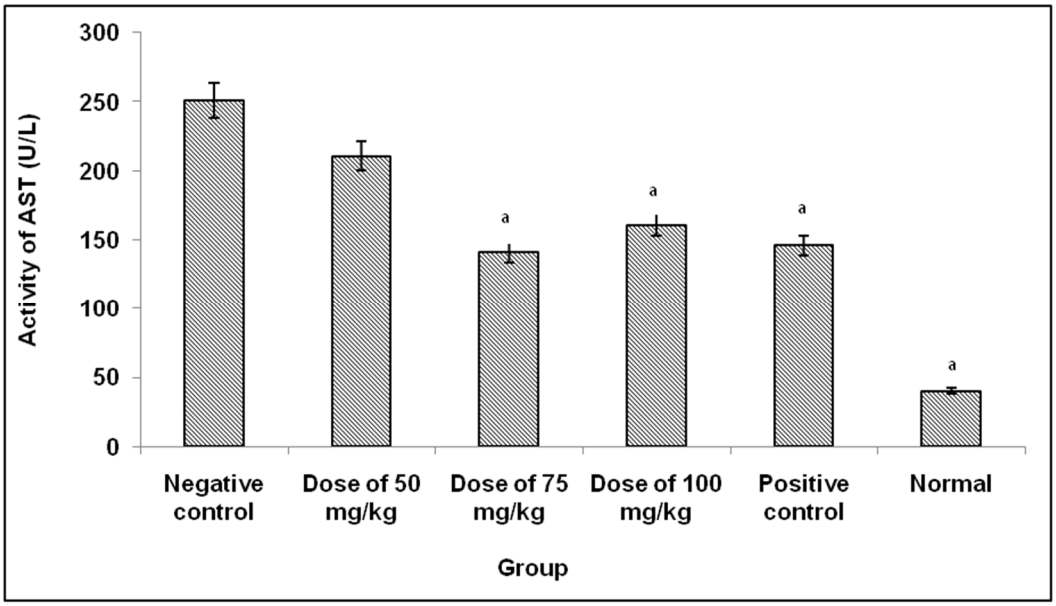


Fig. 3: Activity of ALT and AST from the rats on the 16th day that have been induced by rifampicin and isoniazid

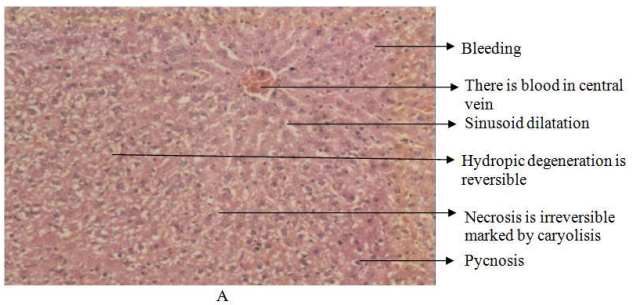
Based on table 3 and fig. 3, ALT of the negative control group increased significantly due to induction of rifampin and isoniazid compared to normal group ($p<0.05$). Administration combination of extracts at the dose of 50 mg/kg could not prevent elevation of ALT. Whereas at the doses of 75 and 100 mg/kg, the combination of extracts was able to prevent increasing of ALT compared to negative control group ($p<0.05$). Moreover, the ALT value of those groups was the same as normal control.

It means that groups at the doses of 75 and 100 mg/kg had hepatoprotective activity. Besides ALT, AST increased significantly compared to normal group ($p<0.05$). Administration combination of extracts at the dose of 50 mg/kg could not prevent elevation of AST. Whereas at the doses of 75 and 100 mg/kg, the combination of extracts was able to prevent the elevation of AST compared to negative control group ($p<0.05$).

Histopathology

Based on table 3 and fig. 3, ALT of the negative control group increased significantly due to induction of rifampin and isoniazid compared to normal group ($p<0.05$). Administration combination of extracts at the dose of 50 mg/kg could not prevent elevation of ALT. Whereas at the doses of 75 and 100 mg/kg, the combination of extracts was able to prevent increasing of ALT compared to negative control group ($p<0.05$). Moreover, the ALT value of those groups was the same as normal control. It means that groups at the doses of 75 and 100 mg/kg had hepatoprotective activity.

Besides ALT, AST increased significantly compared to normal group ($p<0.05$). Administration combination of extracts at the dose of 50 mg/kg could not prevent elevation of AST. Whereas at the doses of 75 and 100 mg/kg, the combination of extracts was able to prevent the elevation of $AST_{compared}$ to negative control group ($p<0.05$)



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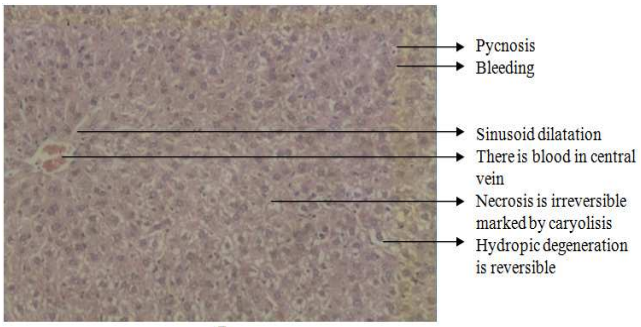

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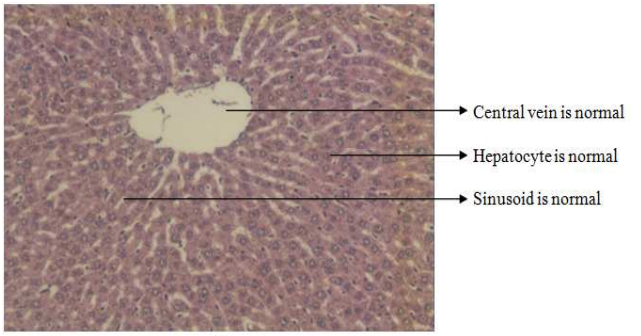

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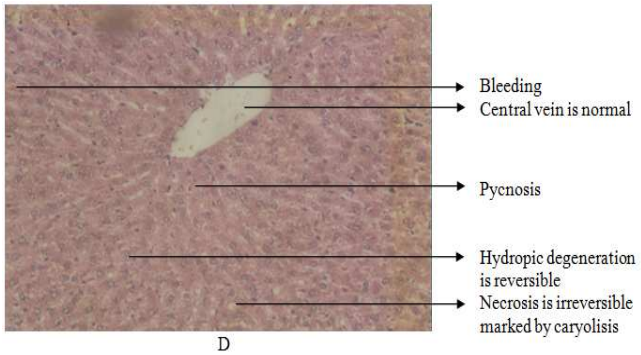

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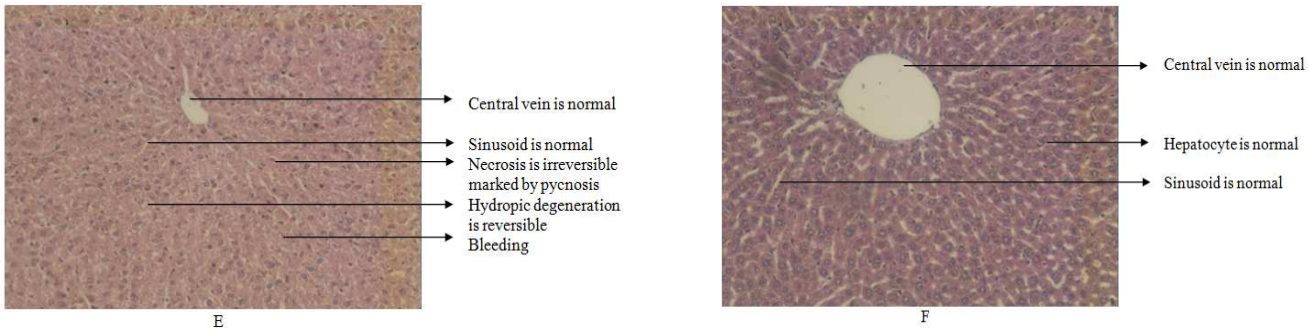

Fig. 4: Histopathology of the liver cell (10x10); (A) negative control; (B) dose of 50 mg/kg; (C) dose of 75 mg/kg; (D) dose of 100 mg/kg; (E) positive control; (F) normal control

Histopathology result showed that there is blood in a central vein in negative control and group

at the dose of 50 mg/kg (fig. 4). Besides that, there is hydropic degeneration and necrotic in the liver cells. It indicates injury in the liver. In the groups at the doses of 75, 100 mg/kg, positive control and normal control, there are no either blood in a central vein or hydropic degeneration and necrotic in liver cells. It means that combination of ethanol extract of *C. fel-terrae* and rhizome of *C. heyneana*at the doses of 75 and 100 mg/kg pose hepatoprotective activity.

DISCUSSION

Rifampin and isoniazid are first line therapy in tuberculosis disease [19-20]. The combination of these drugs in the treatment of tuberculosis disease will increase the risk of hepatotoxicity such as hepatitis [2]. Isoniazid hepatotoxicity is caused by metabolism in the liver which generates some metabolites such as hydrazine, acetylhydrazine, and other hydrazine metabolites that are free radicals [20]. Virtually CYP1A2 has a function to detox hydrazine, however, isoniazid hampers its activity. Rifampin is a strong inducer of the CYP450 system that can increase production of metabolites from other drug which is given concomitantly. Rifampin is able to elevate activity of CYP2E1 that relate to increasing of hydrazine production while it is combined with isoniazid [21]. Hydrazine lower antioxidant activity of glutation peroxidase as well as catalase. Next hydrazine will accelerate lipid peroxidation and cause hepatotoxicity [1].

Hepatotoxicity that is caused by enzyme inducer like rifampin can cause increasing in liver weight, hepatocellular hypertrophy, cell proliferation, and, frequently in long-term (lifetime) studies, hepatocarcinogenesis. These changes may be induced through a common mechanism of action involving activation of the nuclear hormone receptors constitutive androstane receptor (CAR), pregnane X receptor (PXR), or peroxisome activated receptor alpha (PPARα) [22].

C. heyneana contains curcuminoid, which is comprised of curcumin, bisdemethoxycurcumin and desmethoxycurcumin. Curcumin is traditionally known having some effects totreat some diseases in human [23]. Curcumin is able to up-regulation of antioxidant enzyme gene expression, activation of the expressed genes and increase in the availability of glutathione (GSH) [24-25]. Curcuminoid is capable to scavenging the radical acetyl hydrazine and hydrazine which is generated by metabolism of isoniazid [26].

Methanolic extract of *C. fel-terrae* known contains alkaloids, cardiac glycosides, terpenoids, reducing sugar, tannins, phenolic, flavonoids and steroids [27]. Alkaloids in some plants known have significant cytoprotective effect against oxidative stress [28].

CONCLUSION

The combination of ethanolic extract of *C. fel-terrae* and *C. heyneana* can be considered as complement therapy for preventing liver injury which is caused by consuming anti-tuberculosis. Because combination at the doses of 75 and 100 mg/kg is able to protect the liver from damage induced by rifampin and isoniazid. The research can be continued to formulate the dosage form of these extracts.

ACKNOWLEDGEMENT

This research was supported by TALENTA Research Grants (Research No. 6051/UN5.1. R/PPM/2016) from the Universitas Sumatera Utara Indonesia.

CONFLICT OF INTERESTS

Declared none

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How to cite this article

- Marianne, Jessy Chrestella, Maria Andriani Ginting, Aminah Dalimunthe, Rosnani Nasution. Hepatoprotective activity combination of *Curanga fel-terrae* Lou leaves and *Curcuma heyneana* valeton and zijprhizome in rat induced by a combination of rifampin and isoniazid. Int J Pharm Pharm Sci 2017;9(5):23-28.