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The Activity of Purple Sweet Potato Extract on Antituberculosis-Induced Liver Toxicity

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Abstract

BACKGROUND: The proportion of antituberculosis-induced liver injury on tuberculosis patients showed a relatively high incidence in many countries. Hepatic damage induced by antituberculosis drugs might potentially fatal. Isoniazid (INH) and rifampicin (RIF) are two main components of antituberculosis with crucial role for the incidence of liver injury. One of the herbal remedies that pose hepatoprotective action is purple sweet potato. Hepatoprotective action of purple sweet potato extract has been proved to pose antioxidant and anti-inflammatory activity.

AIM: This study was designed to analyze the effect of purple sweet potato extract on rat interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) level, as well as liver histopathology feature in hepatic injury induced by INH-RIF.

METHODS: This study was a randomized posttest-only control group design. Male Wistar rats (*Rattus norvegicus*), age 8–12 weeks, weight 180–220 g were included in this research (divided into three groups). Purple sweet potato extract was produced by maceration technique. IL-6 and TNF-α level was measured by enzyme-linked immunosorbent assay, whereas liver histopathology examination was performed with hematoxylin and eosin staining. Statistical analysis was performed using one-way ANOVA and *post hoc* test.

RESULTS: Liver IL-6 level in the normal, control, and treatment groups was 2.272±0.473, 3.315 ± 0.536, and 2.548 ± 0.304, respectively ($p < 0.001$). Liver TNF-α level in the normal, control, and treatment groups was 26.476 ± 1.681, 48.584 ± 1.359, and 32.547 ± 1.528, respectively ($p < 0.05$). Histopathology feature of the liver in the control group showed significant liver congestion, liver degeneration, liver necrosis, and infiltration of inflammatory cell. Otherwise, histopathology feature of the liver in the treatment group showed minimal lesion.

CONCLUSIONS: Purple sweet potato ethanol extract lowered the liver concentration of IL-6 and TNF-α, as well as improving liver damage in Wistar rats induced with isoniazid and rifampicin.

Introductions

Isoniazid (INH) and rifampicin (RIF) are two main components of the recommended antituberculosis treatment widely used today. These drugs possess a crucial role on the existence of liver damage induced by antituberculosis drugs. The incidence of antituberculosis-induced liver injury in several countries varies between 15% and 35%. The mechanism responsible for liver damage is related to oxidative stress and inflammation process. INH metabolism results in several toxic metabolites, namely hydrazine and acetyl hydrazine. INH, as well as RIF, had also capability to induce CYP2E1 activity and thus lead to an increase of reactive oxygen species production. This in turn results in more creation of toxic metabolites of INH and worsens the liver damage [1], [2], [3].

The excessive formation of free radical accompanied by lack of defense mechanism from endogenous antioxidants would promote oxidative stress condition. Oxidative stress might induce several cellular effects such as lipid peroxidation, protein modification, enzyme inactivation, and DNA damage [4].

Oxidative stress resulted from free radical accumulation might induce inflammation in the liver through nuclear factor kappa B (NF-κB) pathway by stimulating inhibitory kappa B kinase (IκK). Inflammation might also be resulted from the binding of INH metabolite with the lysine residue on the liver. The existence of inflammation was identified from the enhanced pro-inflammatory markers in the liver, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). This was also identified from the liver histopathology features, namely necrosis and lymphocyte infiltration on INH-RIF-induced rats [3], [4].

To date, some traditional medicines (such as curcumin and silymarin) had been proved to be effective for the management of many liver injury cases. This showed that herbal medicines had the potential for alleviating liver injury. Therefore, it is very important to explore other potential herbal remedies which possess hepatoprotective activity, one of which is purple sweet potato.

Purple sweet potato extract showed a hepatoprotective effect on liver toxicity induced by acetaminophen, ethanol, carbon tetrachloride (CCl_4), dimethylnitrosamine (DMN), and D-galactosamine. This effect was identified from its capability of decreasing serum aspartate aminotransferase and alanine aminotransferase level, as well as improving liver injury histopathologically. The hepatoprotective action of purple sweet potato was strongly related to its major secondary metabolite content (its active substance), namely anthocyanins. Anthocyanins were included in flavonoid class of secondary metabolite, which had been proved to possess both antioxidant and anti-inflammatory effects [5], [6], [7].

Many evidences had proved the anti-inflammatory action of purple sweet potato extract and its major active substance (anthocyanins). A previous study demonstrated that purple sweet potato reduced the level of pro-inflammatory cytokine TNF-α, IL-1β, and IL-6 in the rat liver after induced with hepatotoxic agents [6]. The pharmacodynamic mechanism of anthocyanin hepatoprotective action had been shown to be associated with its inflammatory action which was resulted from the inhibition of NF-κB signaling pathway. However, the types of hepatotoxic agents in those previous studies were different (acetaminophen, ethanol, carbon tetrachloride, dimethyl nitrosamine, and D-galactosamine). It has been well known that the pathogenesis of liver injury was strongly related to the type and characteristic of the causative agents [6].

Unlike INH-RIF, some hepatotoxic agents (carbon tetrachloride, DMN, and D-galactosamine) are only used for research purposes (*in vivo* study), never been found in a real setting in humans. Otherwise, acetaminophen-induced liver toxicity (like antituberculosis-induced liver toxicity) was a common case in practice, but the mechanism of liver injury might not be exactly the same as INH-RIF toxicity. Mitochondrial oxidative stress was considered to be the major mechanism responsible for the acetaminophen-induced liver damage, which was related to the acetaminophen metabolism process. Inflammation signs might also be found in its histopathology features, as in antituberculosis-induced liver toxicity. However, unlike antituberculosis, there has been a specific antidote for liver toxicity induced by acetaminophen, namely N-acetyl cysteine. Another hepatotoxic agent, ethanol, had been widely known to be responsible for liver damage. Ethanol-induced liver toxicity might manifest histopathologically as steatosis (fat degeneration), inflammation (necrosis), and liver fibrosis. Purple sweet potato extract (contain anthocyanins) had performed hepatoprotective effect on liver toxicity induced by those hepatotoxic agents [5], [6], [7]. Therefore, purple sweet potato extract might also be considered to be potential for liver protection in INH-RIF toxicity. However, this required a scientific research for confirmation.

To date, there has been no study investigating the effect of purple sweet potato extract to several inflammatory markers (such as IL-6 and TNF-α level, as well as histopathology feature in the liver) specifically on liver toxicity induced by INH-RIF. Those markers have been shown to increase in liver inflammation resulted from INH-RIF administration. Therefore, it was very important to investigate such topic in order to gain complete understanding regarding the effect of purple sweet potato extract to common inflammatory markers (such as IL-6 and TNF-α as well as histopathology feature of the liver) in liver injury induced by INH and RIF.

Methods

Study design

This study was an experimental study with randomized posttest-only control group design. The study was conducted at the Integrated Biomedical Laboratory of Medical Faculty, Udayana University, Bali. The study protocol had been approved by the Animal Ethical Committee of Veterinary Faculty, Udayana University, Bali, Indonesia (Approval number: 3178/UN14.2.9/PD/2019).

Samples

Our study included thirty rats (*Rattus norvegicus*) strain Wistar, male, age 8–12 weeks, weight 180–220 grams. The minimum number of samples was 30 samples. The samples were then divided into three groups:

1. Normal group (only received aqua bidestilata water);
2. Control group (received only combination of INH and RIF, without administration of purple sweet potato extract);
3. Treatment group (received combination of INH-RIF and purple sweet potato extract).

Preparation of purple sweet potato extract

Purple sweet potato was extracted using maceration method. The solvent applied in the extraction process was 95% ethanol.

Induction and intervention

The combination of INH and RIF was administered intragastrically for 4 weeks (28 days), whereas the purple sweet potato extract was administered intragastrically 1 week prior to INH-RIF administration and continuously administered for 5 weeks (35 days). The dosage of INH-RIF combination

was 500 mg/kg/day, whereas the dosage of purple sweet potato extract was 1 gram/kg/day [8]. The treatment dose was based on our preliminary study [8].

Assessment of interleukin-6 and tumor necrosis factor-α level

The IL-6 and TNF-α concentration in the liver was measured using enzyme-linked immunosorbent assay method. The liver histopathology examination was performed with hematoxylin-eosin staining.

Histopathology examination

The histopathological features of the liver evaluated in the study included liver congestion, liver degeneration, liver necrosis, and infiltration of inflammatory cells in the liver. Liver congestion was observed from the hyperemia and dilatation of central vein. Liver degeneration was characterized by the presence of vacuoles in the cytoplasm and the nucleus being pushed to the edge. Liver necrosis was characterized by unclear cell boundaries and nuclear lysis.

Data analysis

Statistical analysis was performed using one-way ANOVA and *post hoc* test. The p-value below 0.05 was considered to be statistically significant.

Results

Interleukin-6 and tumor necrosis factor-α concentration in the liver

The control group showed a significant increase in IL-6 and TNF-α level in the liver compared to the normal group (healthy). The treatment group showed a significant decrease level of IL-6 and TNF-α in the liver compared to the control group. Liver IL-6 level in the normal, control, and treatment groups were 2.272 ± 0.473; 3.315 ± 0.536; 2.548 ± 0.304, respectively ($p < 0.001$). Liver TNF-α level in the normal, control, and treatment groups were 26.476 ± 1.681; 48.584 ± 1.359; 32.547 ± 1.528, respectively ($p < 0.05$) (Table 1). Post hoc analysis for IL-6 and TNF-α level could be seen in Tables 2 and 3. The result of post hoc analysis also confirmed IL-6 and TNF-α level in the treatment group were significantly lower than in the control group ($p < 0.05$).

Table 1: The level of interleukin-6 and tumor necrosis factor-α in rat liver

Variable	Group, mean ± SD			p
	Normal	Control	Treatment	
IL-6 level (ng/L)	2.272 ± 0.473	3.315 ± 0.536	2.548 ± 0.304	<0.001*
TNF-α level (ng/L)	26.476 ± 1.681	48.584 ± 1.359	32.547 ± 1.528	0.006*

*Statistically significant. IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-α, SD: Standard deviation.

Histopathology examination

The histopathology examination of the liver evaluated in the samples congestion, degeneration, necrosis, and inflammatory cell infiltration. Each sample was evaluated based on the area of lesion (focal, multifocal, or diffuse) on five fields of view. Histopathology feature of the liver in the control group showed significant liver congestion, liver degeneration, liver necrosis, and infiltration of inflammatory cell. The histopathology feature of the liver in the treatment group showed minimal congestion, degeneration, necrosis, and inflammatory cell infiltration (Figure 1).

Discussions

This study had proved that administration of INH-RIF combination would lead to an increased level of TNF-α and IL-6 in the rat liver. This was similar to results from other previous studies on liver toxicity induced by either RIF alone; combination of INH and RIF; combination of INH, RIF, and pyrazinamide (PZA); or combination of INH, RIF, PZA, and ethambutol (ETB). Those *in vivo* studies had confirmed the toxic effect of antituberculosis drugs on the liver, one of which was an enhanced level of pro-inflammatory cytokines such as TNF-α and IL-6. However, the dosage and the component of antituberculosis regimen, as well as the duration of antituberculosis administration, varied among studies [3], [9], [10], [11], [12].

Table 2: *Post hoc* analysis for interleukin-6 level in the rat liver

Variable (mean ± SD)	Compared group	Mean difference	p	95% CI	
				Lower	Upper
IL-6 level (ng/L)	Normal versus control	−1.044	< 0.001*	−1.480	−0.607
	Normal versus treatment	−0.277	0.203	−0.713	0.159
	Control versus treatment	0.767	0.001*	0.331	1.204

*Statistically significant. IL-6: Interleukin-6, SD: Standard deviation, CI: Confidence interval.

This research also revealed that INH-RIF administration would lead to liver damage on rats, which was identified from the histopathology examination. This was in line with other previous studies which performed toxic effect of antituberculosis in rat liver whether in single or combination. Previous studies had confirmed the evidence of inflammation which was characterized by histopathology feature of the liver including necrosis, congestion, degeneration, or infiltration of inflammatory

Table 3: *Post hoc* analysis for tumor necrosis factor-α level in the rat liver

Variable (mean ± SD)	Compared group	Mean difference	p	95% CI	
				Lower	Upper
TNF-α level (ng/L)	Normal versus control	−22.108	0.002*	−35.424	−8.793
	Normal versus treatment	−6.071	0.356	−19.386	7.245
	Control versus treatment	16.038	0.020*	2.722	29.353

*Statistically significant. TNF-α: Tumor necrosis factor-α, SD: Standard deviation, CI: Confidence interval.

cells in the liver. However, the dosage, component of combination, and duration of antituberculosis administration varied among studies [13], [14], [15], [16].

A study conducted by Hassan *et al.* (2016) revealed an increased level of liver TNF-alpha and IL-6, as well as liver damage on rats induced by INH 400 mg/kgBW for 14 days. The liver damage was identified from the liver inflammation, necrosis, and steatosis [4]. A similar finding was reported by Mawarti *et al.* (2017). The study revealed an increased level of TNF-α and IL-6 in the rats' liver after administration of INH and RIF. The study reported an increased level of IL-6 on rat liver after INH and RIF administration 50 mg/kgBW [9]. Study conducted by Liu *et al*. confirmed an enhanced level of IL-6 in the rat liver after received combination of antituberculosis INH (100 mg/kgBW)/RIF (250 mg/kgBW)/ PZA (50 mg/kgBW) for 30 days [3]. A study by Adaramoye *et al.* (2016) reported a similar result. It reported increased level of IL-6 and TNF-alpha in rat liver after administration of antituberculosis combination contained INH (5 mg), RIF (10 mg), PZA (15 mg), and ETB (15 mg) for 8 weeks [10]. Other studies conducted by Hussain *et al.* (2012), Miglani *et al*. (2016), and Liu *et al*. (2017) found histopathology damage in the liver after administration of antituberculosis INH, RIF, and PZA. A research by Miglani *et al.* (2016) had performed a similar result after receiving INH, RIF, and PZA as many as 27 mg, 54 mg, and 135 mg per kgBW, respectively, for 30 days. Histopathology features evaluated in the study were necrosis, infiltration of inflammatory cells, and degeneration [11]. A research by Hussain *et al*. (2012) and Liu *et al*. (2017) confirmed the liver injury after administering the combination of INH/RIF/PZA which was observed from histopathology examination. However, the dosage of antituberculosis used on both studies varies. Research by Hussain *et al*. (2012) administered combination of 7.5 mg of INH, 10 mg of RIF, and 35 mg of PZA on rats for 35 days; whereas study by Liu et al. (2017) administered 100 mg of INH, 250 mg of RIF and 50 mg of PZA on rats for 30 days. The histopathological feature evaluated in both studies were liver necrosis, degeneration, and infiltration of inflammatory cells [3], [12]. A study performed by Sankar *et al*. (2015) and Rao *et al.* (2012) revealed histopathology injury of the liver, namely necrosis, fat degeneration, lymphocyte infiltration, loss of cell membrane integrity, and hepatocellular enzyme leakage on rats after receiving INH and RIF combination as many as 50 mg/kgBW for 30 days [13], [14]. Another study conducted by Shih *et al*. (2013) reported a similar result which was identified from the histology activity index of the rat liver after INH and RIF administration 50 mg and 100 mg per kgBW, respectively, for 3 weeks [15], [16].

Prolonged administration of INH and RIF would potentially lead to inflammation directly or through the oxidative stress pathway. Inflammation induced by INH or combination of INH-RIF might be produced directly due to the binding of INH metabolites into the liver macromolecules (covalently bind to lysine residue on liver protein). This would induce inflammatory response in the liver and enhance the level of inflammatory markers in the liver, namely TNF-α, IL-1β, and IL-6 [4]. ROS generation, as the result of INH administration, might be the result of increased CYP2E1 activity. ROS formation would potentially induce inflammation by activating NF-κB. ROS promote the phosphorylation of inhibitor of NF-κB (IκB) by IκK and thus would release IκB from NF-κB. Subsequently, IκB would be degraded by proteasome whereas NF-κB would activate transcription of pro-inflammatory genes including cytokine TNF-α and IL-6. IL-6 and TNF-α are released in many inflammatory disorders. The binding of IL-6 to receptor would promote signaling pathway via Janus kinase-signal transducer and activator transcription (JAK-STAT) and promote subsequent inflammation [17], [18]. Otherwise, TNF-α binding to its receptor (TNFR1), specifically in its death domain (TRADD), would recruit TNF-α receptor-associated factor 2 (TRAF2), receptor-interacting protein (RIP), and apoptosis inhibitor. Thus, it would result in the formation of TNF-α-induced signaling complex 1. This complex would then activate NF-κB (by activating IκK) or c-Jun N-terminal kinase (JNK) pathway. Activation of IκK would phosphorylate IκB and thus release it from NF-κB. In turn, it would activate NF-κB and promote the transcription of many pro-inflammatory genes. Activation of JNK would phosphorylate cJun protein and subsequently combine with cFos to generate activator protein 1 (AP-1). This in turn would induce the transcription of several inflammatory proteins [19], [20].

Our study revealed the effect of purple sweet potato ethanol extract on decreasing the level of TNF-α and IL-6 in the liver, as well as ameliorating liver injury induced by INH and RIF on rats. The administration of purple sweet potato ethanol extract reduced the concentration of IL-6 and TNF-α in the liver into the level which was statistically insignificant comparing to the normal (healthy) group. This confirmed the beneficial effect of purple sweet potato extract on suppressing inflammation related to toxic effect of antituberculosis in the liver.

However, no previous research had studied the effect of purple sweet potato ethanol extract on liver inflammation related to INH and RIF toxicity. Some previous studies reported the activity of purple sweet potato ethanol extract on liver toxicity induced by other substances such as DMN, ethanol, and acetaminophen. A study performed by Choi *et al*. (2010) showed a decreased level of TNF-α and IL-6 in the liver after administration of purple sweet potato extract on liver damage induced by DMN [21]. Another study by Ezzat *et al*. (2016) revealed a similar result.

Purple sweet potato extract had been proved to contain anthocyanins as the major active substances.

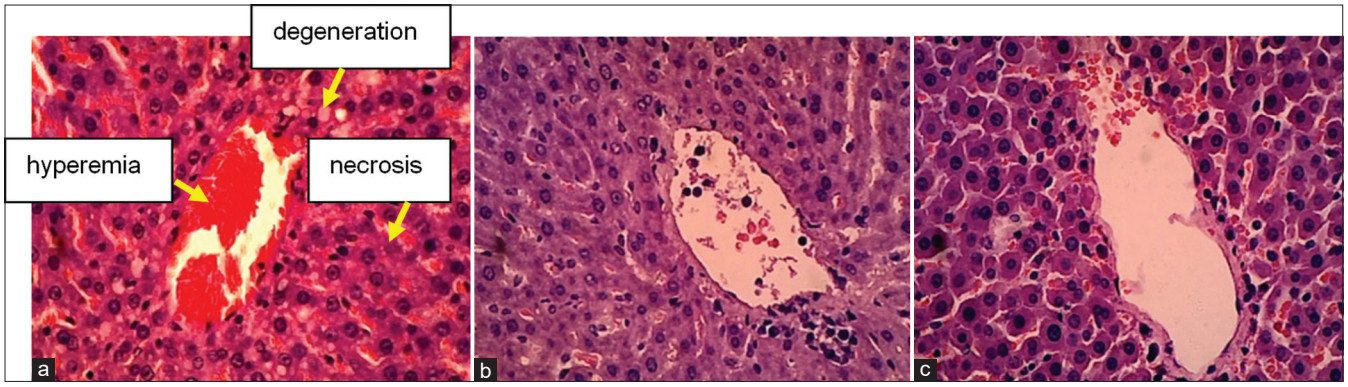

Figure 1. Histopathology feature of the liver (H and E, ×400). (a) Control group, (b) Treatment group, (c) Normal group

Our study prepared purple sweet potato ethanol extract from local plants. The composition of anthocyanins in our extract was 146 mg/mL [5]. Anthocyanins are generally known as natural water-soluble pigments (mostly in red, blue, or purple pigment) which belong to the phenolic groups (specifically flavonoid group). The common types of anthocyanins found in purple sweet potato are cyanidines and peonidines. Anthocyanin-contained plants had been widely studied for their medicinal purposes, one of which was for liver protection. A study conducted by Ezzat *et al.* (2016) administered rosella extract (which also contained anthocyanins) on liver injury induced by thioacetamide for 4 weeks. The study demonstrated the reduction of some inflammatory markers, namely TNF-α, IL-6, interferon-γ, and NF-κB, after rosella extract administration [22].

There has been very limited studies that reported the effect of purple sweet potato extract on liver toxicity induced by antituberculosis. However, several studies had confirmed the hepatoprotective effect of purple sweet potato extract on liver toxicity induced by other substances including ethanol, acetaminophen, DMN, and thioacetamide, which were detected from its activity in improving liver damage [7], [21], [22]. A study performed by Choi *et al.* (2009) revealed the effect of purple sweet potato extract on ameliorating liver injury induced by acetaminophen [21]. A study by Choi *et al.* (2010) reported a similar result, but the liver injury was induced by DMN [22]. A study conducted by Sun *et al*. (2014) also confirmed a similar result. However, the liver toxicity was induced by ethanol [7]. Another research revealed improvement on liver histopathology regarding the administration of purple sweet potato extract on rats which underwent ovarectomy [23].

The anti-inflammatory action of purple sweet potato is widely known to be related to its activity on NF-κB. Moreover, anthocyanins could also modulate several signaling pathways such as mitogen-activated protein kinase (MAPK) or phosphatidylinositol 3-kinase/protein kinase B (PI3k/Akt). This is related to antioxidant and anti-inflammatory effect of anthocyanins [19], [20].

A previous study had proved the role of PPAR-α (peroxisome proliferator-activated receptor) on liver inflammation related to INH and RIF toxicity [19]. A study conducted by Artini *et al*. (2020) reported that purple sweet potato extract potentially activated PPAR. Generally, PPAR is a transcription factor for many anti-inflammatory and antioxidant proteins. Activation of PPAR might directly promote transcription of target gene (such as hsp70) through interaction with PPAR response element (PPRE). The role of PPAR on inflammation process might also occur indirectly by affecting other transcription factors such as NF-κB, MAPK, and others. Activation of PPAR would inhibit the NF-κB activity through several pathways, one of which was by binding to p65 subunit of NF-κB or by increasing the expression of IκB (inhibitor NF-κB) protein. PPAR would also inhibit NF-κB activity by inactivating glycogen synthase kinase 3β or inactivating coactivator p300. Inactivation of p300 might result in the decreased acetylation of p65 of NF-κB. Subsequently, this would lead to the decreased transcription of pro-inflammatory protein (TNF-α, IL-6, IL-1β, cyclooxygenase, phospholipase A2, inducible nitric oxide synthase, vascular cell adhesion molecule 1, intercellular adhesion molecule 1, and others) [17], [18].

Conclusions

Purple sweet potato ethanol extract potentially suppressed liver inflammation on antituberculosis-induced liver toxicity, which was presented by the decrease of TNF-α and IL-6 concentration in the liver, as well as improvement of liver damage.

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