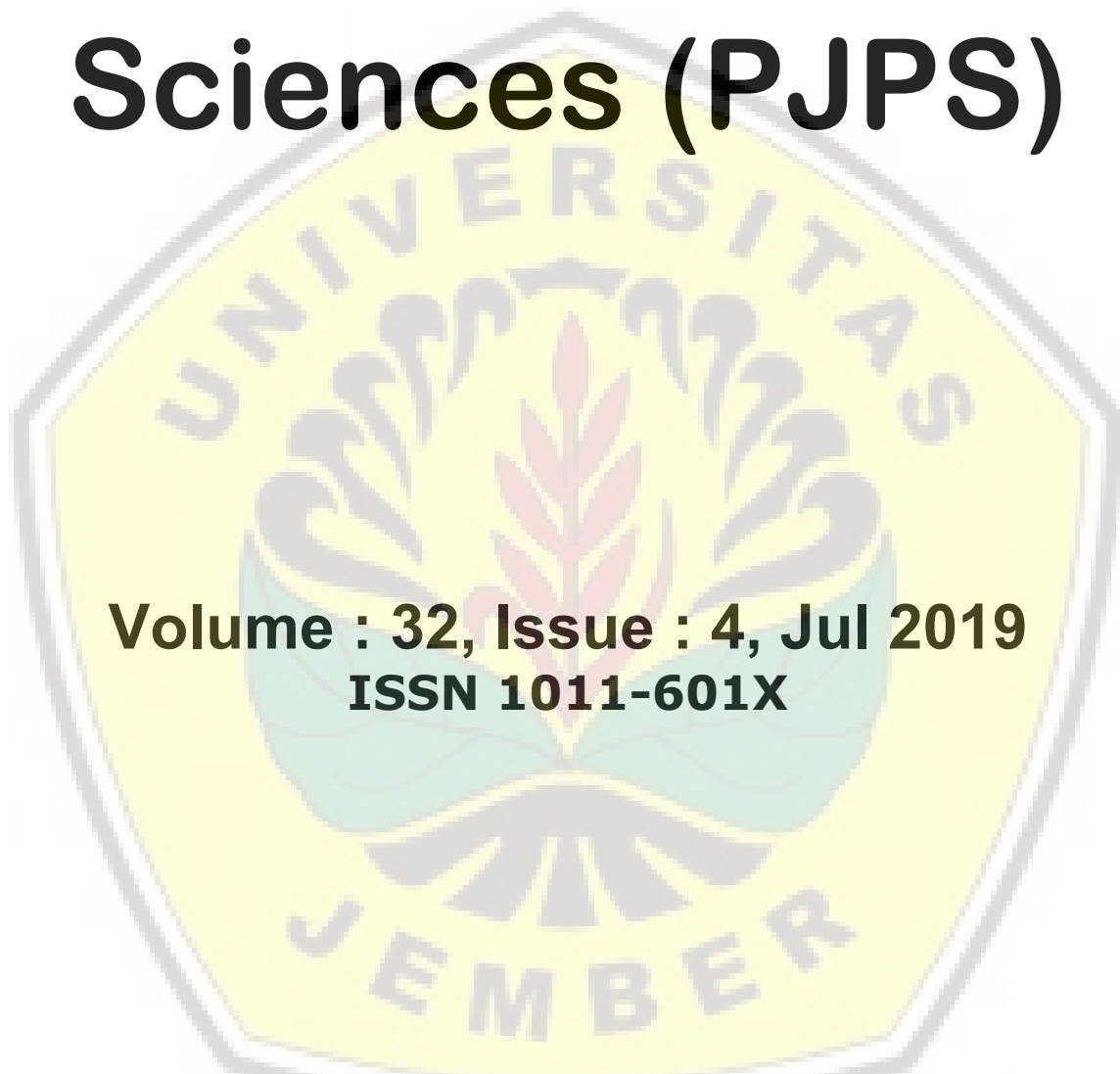


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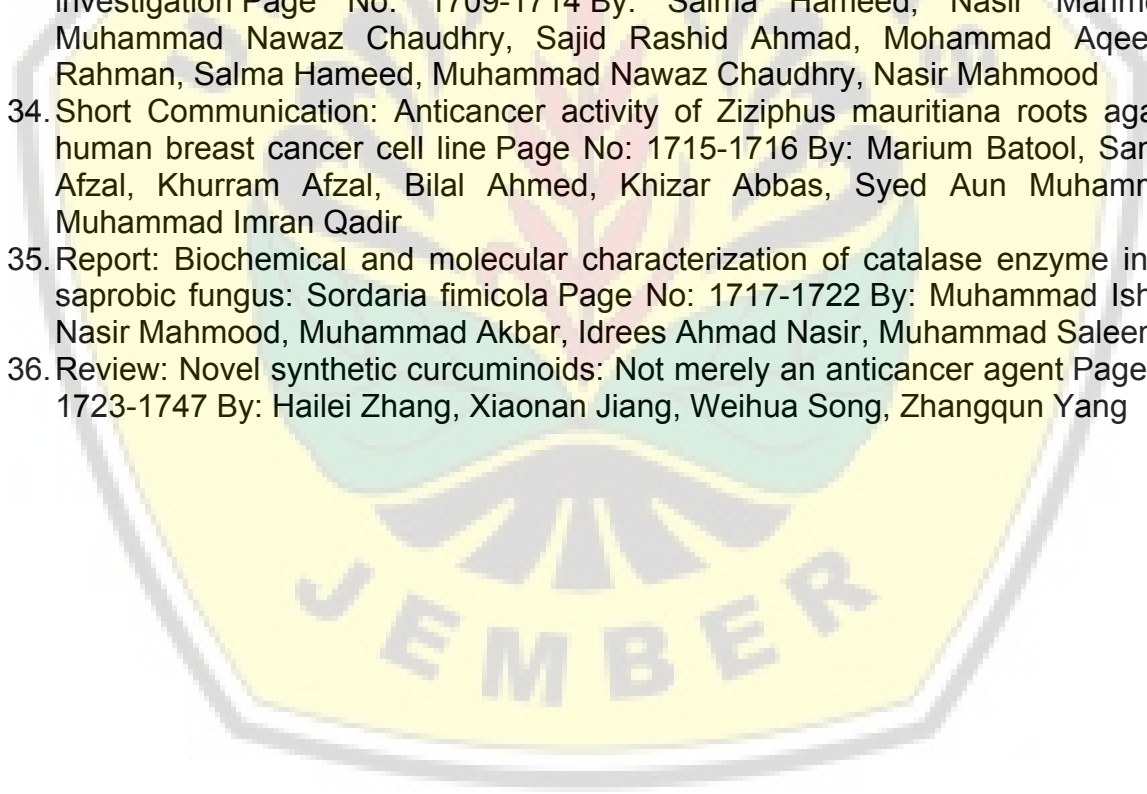
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Antihyperalgesia potency of *Zingiber officinale* var. *Rubrum* in inflammatory and neuropathy-induced chronic pain condition in mice

Fifteen Aprila Fajrin¹, Azham Purwandhono², Fransisca Maria Christianty¹, Gati Dwi Sulistyaningrum¹, Afifah¹, Nidia Imandasari¹ and Tsabit Barki¹

¹Faculty of Pharmacy, University of Jember, East Java, Indonesia

²Faculty of Medicine, University of Jember, East Java, Indonesia

Abstract: Chronic inflammation and neuropathic pain are classified into chronic pain. Until now there are so many drugs that have been used for chronic pain but the effectiveness still lower. One of the plants that are commonly used for medicine in Indonesia is red ginger (*Zingiber officinale* var. *rubrum*). This study was aimed to analyze the component of red ginger oil and proved its antihyperalgesia potency in chronic pain using two models, inflammatory pain and neuropathy pain. Forty-eight mice were divided into 2 groups i.e. inflammatory and neuropathy. Each group was divided into 6 subgroups (@4 mice) i.e. for inflammatory model (sham, negative control, red ginger oil doses 100, 200, 400 and 600 mg/kg) and for neuropathy model (sham, negative control, red ginger oil doses 100, 200, 400 and 600 mg/kg). Inflammatory model was induced using Completed Freud's Adjuvant (CFA) 40 µl intraplantar. Neuropathy model was induced using Partial Sciatic Nerve Ligation (PSNL). At day-7, all groups were given orally treatment, once daily for seven days. The latency time toward thermal stimulus and plantar thickness were measured at day 0,1,3,5,7,8,10,12 and 14 after induction. Quality of red ginger oil was standardized by Indonesia standard (SNI 06-1312-1998). The red ginger oil compound was identified by GC/MS. The result showed that red ginger oil was qualified based on SNI 06-1312-1998. Red ginger oil 200 mg/kgBW and 400mg/kgBW administration in mice gave the best result in prolong the latency time toward thermal stimulus using hot plate and significantly different with inflammatory and neuropathy group. From GC/MS analysis, camphene was known as the highest compound of red ginger oil that might be important for its antihyperalgesia effect. The conclusion of this study that red ginger oil have antihyperalgesia activity in mice with chronic pain and could be developed further to be antihyperalgesia.

Keyword: Chronic pain, hyperalgesia, CFA, PSNL, red ginger oil.

INTRODUCTION

Pain is a multidimensional experience that affect to both sensory and emotional aspect of human being. Chronic pain, a pain with duration more than 6 months, usually follows chronic or degenerative diseases such as diabetes mellitus, cancer, chronic inflammation, infection and many else. Approximately one of five populations is diagnosed by chronic pain (van Hecke *et al.*, 2013). The prevalence rate was different in every country. The estimation of chronic pain incidence were 20.2% in Denmark, 22.1% in Australia, 31.4% in Sweden, 35.1% in Finland, 35.5% in the USA and 46% in Israel (Igumbor *et al.*, 2011).

Until now, treatments for chronic pain are still a challenge because of its lower effectiveness and higher side effects (Baron *et al.*, 2010; Cole, 2002). Without an appropriate treatment, it will be difficult for patients to improve their quality of life. Many patients with chronic pain get inability to do their daily activities and some of them loss their job. This condition may lead to stress and depression condition that enhance the pain threshold as well. Because of all of this, the health financial cost also increases. In

Europe the cost for chronic pain is 200 billion Euro for a year and 635 billion US dollar for a year in United States (van Hecke *et al.*, 2013).

Regarding on pathophysiology, chronic pain are triggered by inflammation and neuropathy condition. Complex pathophysiology of chronic pain involves the increasing of oxidative stress. Peripheral nerves injuries by chronic inflammation and neuropathy cause increasing of super oxides (SO) and activate peroxynitrite (PN) (Singh *et al.*, 2014). The higher accumulation of PN triggers some pathways, such as Gamma Amino Butyric Acid (GABA), Cyclooxygenase (COX), glutaminergic neurotransmission, Protein Kinase C (PKC), Transient Receptor Protein (TRP) channel, cytokine and Mitogen-Activated Protein Kinase (MAPK) and then stimulates central sensitization in chronic pain (Farmer *et al.*, 2012).

Red ginger is one of the species from ginger that have been used by Indonesian people as treatment in many diseases (Shimoda *et al.*, 2010). Red ginger had an antioxidant effect higher than ginger (Obloh *et al.*, 2012a). Based on previous results, red ginger had higher ability to inhibit lipid peroxidation in rat's brain than ginger, represent of the previous statement (Obloh *et al.*, 2012b).

*Corresponding author: e-mail: fiezz_15@yahoo.co.id

The active compounds of ginger include volatile oil and pungent phenol compounds such as gingerol and shogaol (Hernani, 2011). Red ginger oils composition are consisted of essential oils, such as cineol and zingiberen. Essential oils from red ginger have been known as compound that responsible for antioxidant activity (Quintnas-Junior *et al.*, 2013). Based on relationship between pathophysiology of chronic pain with oxidative stress, it was possible to block central sensitization by antioxidant activity (Anfenan, 2014). This study was aimed to analyze the component of red ginger oil and proved its antihyperalgesia potency in chronic pain using two models, inflammatory pain and neuropathy pain.

MATERIALS AND METHODS

Forty-eight of 8-week-old mice (male) were used for the experiment. They were purchased and kept in the Animal House, Faculty of Pharmacy, University of Jember, East Java, Indonesia. The temperature of the room was maintained at 26-28 °C with a 12-hour light/12-hour dark cycle.

Red ginger (10 month) was purchased from farmer group "PeciFarm" in Kencong, Jember, East Java, Indonesia. CFA (Completed Freud's Adjuvant) was purchased from Sigma Chemical Co USA. For neuropathy pain, we used suture 8/0 (Ethicon) and silk suture (One Med).

This research was done in Faculty of Pharmacy University of Jember and got the ethical approval from Committee of Ethics from Faculty of Medicine, University of Jember (No: 774/H25.1.11/KE/2016)

Red Ginger Oil Preparation

100-200 g fresh red ginger was prepared in destilator with aquadest (1:2). Distillation process was done in 100-121 °C, for 5-6 hours. Red ginger oil was emulated with tween 0.5% at dose 100, 200, 400 and 600 mg/kgBW.

Red Ginger Oil Specification (SNI 06-1312-1998)

Distillates were analyzed for physic-chemical characteristics, included density, the acid number and the ester number. The analytical method used the national (Indonesia) standard in accordance with the quality standards referred, SNI 06-1312-1998 (Oil of ginger). Experiments were performed with three replications.

GC/MS Analysis for Red Ginger Oil

GC/MS analysis was carried out on GCMS-QP2010 Plus (C146-E087F, Shimadzu, Tokyo, Japan). The sample was detected on a column oven temperature 80 °C and injection temperature 250 °C with total flow 9 ml/min and column flow 1 ml/min. The EI mode for mass spectrometers had ion source temperature of 200 °C and interface temperature of 280 °C. Samples were injected in split mode. Total elution time was 55 min. MS scanning was performed from m/z 40 to m/z 600.

GC/MS Identification of Components

Identification of red ginger oil component was based on computer evaluation of mass spectra of sample from library (WILEY7.LIB). Identification was analyzed by comparison of peaks and retention with standard compound by following the characteristic fragmentation of the mass spectra of compounds.

CFA (Completed Freud's Adjuvant)-induced Inflammatory Pain Model

Twenty-four mice were divided into 6 groups (4 mice in each group) i.e. sham, negative control, treatment (red ginger oil at four different doses: 100, 200, 400 and 600 mg/kgBW). Inflammatory condition was induced by intraplantar injection of CFA. Mice were anesthetized by ether and injected by 40 µl of CFA in intraplantar site. Mice in sham group were injected by 40 µl normal saline. Red ginger oil (in treatment groups) was administrated orally once a day for seven consecutive days, a week after CFA injection. Sham and inflammation control were administrated by tween 0.5%.

PSNL (Partial Sciatic Nerve Ligation)-induced Neuropathy Pain Model

Twenty-four mice were divided into 6 groups i.e. sham, negative control, treatment (red ginger oil at four different doses: 100, 200, 400 and 600 mg/kg). Mice were induced neuropathy with PSNL method. Mice were anesthetized with ether and tied 1/3-1/2 of dorsal portion of sciatic nerve on the left lumbar nerve of mice with 8-0 silk. In sham group, the sciatic nerve was exposed without ligation. Red ginger oil (in treatment groups) was administrated orally once a day for seven consecutive days, a week after PSNL induction. Sham and neuropathic control were administrated by tween 0.5%.

Hyperalgesia and Antinociceptive Response Test

Latency time toward thermal stimulus were measured using hot plate at temperature 50±0.5 °C on days 0 (baseline), 1, 3, 5, 7, 8, 10, 12 and 14. Hyperalgesia responses of mice were showed with licked, flicked or jumped (whichever came first). Paw thickness at the ipsilateral site of mice in inflammatory model was also measured on days 0 (baseline), 1, 3, 5, 7, 8, 10, 12 and 14.

STATISTICAL ANALYSIS

Latency time towards thermal stimulus and paw thickness was expressed as mean ± SEM. The significant differences between injury (inflammatory and neuropathy) and sham group on day 0,1,3,5 and 7 were tested by independent t-test (p<0.05). The significant differences between groups on day 8,10,12 and 14 were tested by one-way ANOVA followed by Tukey's HSD (p<0.05).

RESULTS

Red Ginger Oil Specification

The yield from distillation was 0.43%. Red ginger oil from distillation was analyzed for density, the acid number and the ester number. The result can be shown at table 1.

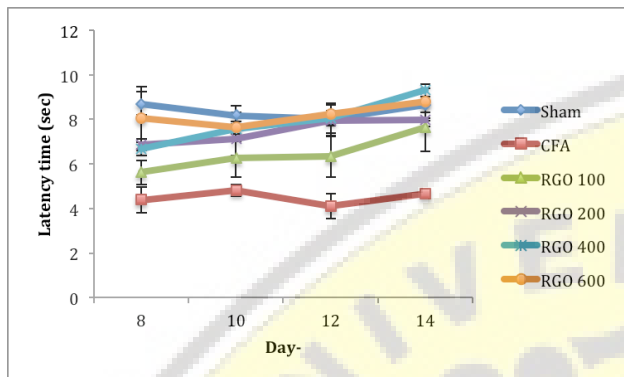


Fig. 1: Average of Latency Toward Thermal Stimulus After Ginger Oil Administration on day 8, 10, 12 and 14. RGO: Red ginger oil

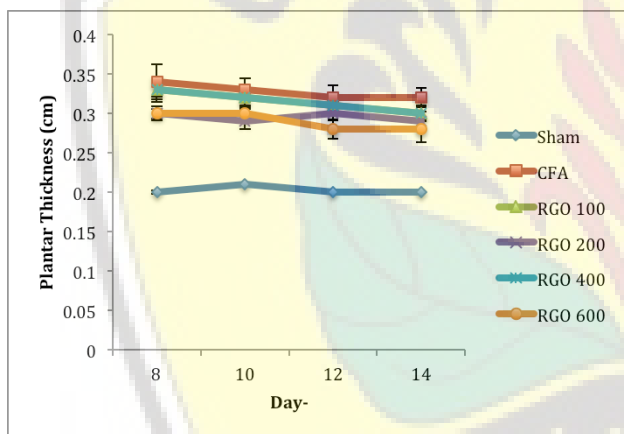


Fig. 2: Average of Paw Thickness of Mice After Red Ginger Oil Administration on day 8, 10, 12 and 14. RGO: red ginger oil

CFA-induced Inflammatory Pain

Table 2 and 3 showed that at baseline (day-0), there was no significant different between the paw thickness and latency time toward thermal stimulus between sham and CFA group ($p > 0.05$). It described that all mice in the same condition at the beginning of the study. One day after CFA induction, the paw thickness of CFA group (0.36 ± 0.01 cm) was significantly bigger than sham group (0.21 ± 0.01 cm). It means that CFA induced inflammatory process that characterized by edema in plantar site. This condition was occurred until day-7 and we concluded that it was a chronic inflammation.

The increasing of paw thickness was followed by the decreasing of the latency time toward thermal stimulus.

One day after CFA induction (table 3), the latency toward thermal stimulus of CFA group (7.13 ± 0.23) was significantly lower ($p < 0.05$) than sham group (8.96 ± 0.76). The latency toward thermal stimulus in CFA group was continued to decrease until day-7. It showed that mice in CFA group in hyperalgesia state.

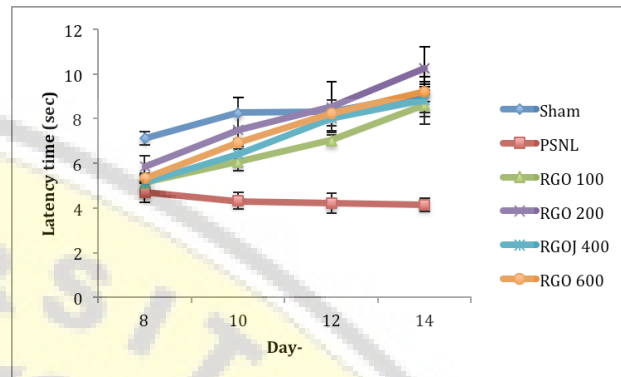


Fig. 3: Average of Latency Toward Thermal Stimulus After Ginger Oil Administration on day 8, 10, 12 and 14. RGO: Red ginger oil

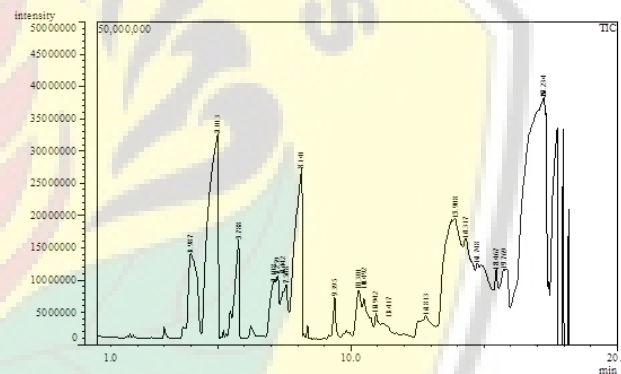


Fig. 4: The Chromatogram Profile of Essential Oil from Red Ginger by GC/MS

PSNL-induced Neuropathy Pain

Table 4 described that previously, there was no significantly different between latency time toward thermal stimulus of PSNL and sham group on day-0 ($p > 0.05$) and this condition was significantly different after PSNL induction. After PSNL induction, the latency toward thermal stimulus in PSNL group significantly decreased ($p < 0.05$), lower than sham group on day-1, 3, 5 and 7 from 8.76 ± 0.29 sec to respectively, 5.11 ± 0.33 sec, 3.94 ± 0.18 sec, 3.32 ± 0.15 sec and 3.13 ± 0.20 sec.

Red Ginger Oil Activity in CFA-induced Inflammatory Pain

Red ginger oil administration for 7 days changed the hyperalgesia response in mice. fig. 1 and table 5 showed that red ginger oil increased latency time toward thermal stimulus by increasing the percentage of latency time toward thermal stimulus compared to CFA group. One day after treatment, latency time toward thermal stimulus

Table 1: Red ginger oil specification

No	Criteria	SNI ^{*)} (06-1312-1998)	Result	Description
1	Color	-	Yellow-red	-
2	Density	0.872-0.889	0.881 g/ml	Qualify
3	The acid number	Max 2	0.202	Qualify
4	The ester number	Max 15	2.0635	Qualify

^{*)} SNI (Standar Nasional Indonesia)

Table 2: The average of paw thickness of mice between cfa and sham groups on day 0, 1, 2, 3, 4, 5, 6 and 7

Group	Average of Paw Thickness of Mice on day- (cm ± SEM)					% Increasing of Paw Thickness On day-7
	0	1	3	5	7	
Sham (N = 4)	0.19±0.01	0.21±0.01	0.19±0.01	0.20±0.01	0.20±0.01	5.26
CFA (N = 20)	0.20±0.01	0.36±0.01*	0.34±0.01*	0.34±0.01*	0.34±0.01*	70.00

Table 3: The average of latency time toward thermal stimulus between CFA and sham groups on Day 0, 1, 3, 5 and 7

Group	Average of Latency Time Toward Thermal Stimulus on day- (cm±SEM)					% Decreasing of Latency Time on day-7
	0	1	3	5	7	
Sham (n = 4)	9.03±0.65	8.96±0.76*	8.36±0.18*	8.98±0.55*	8.42±0.34*	6.76
CFA (n = 20)	9.52±0.43	7.13±0.23	6.98±0.20	6.65±0.25	5.60±0.26	41.18

Table 4: The average of latency time toward thermal stimulus between psnl and sham groups on day 0, 1, 3, 5 and 7

Group	Average of Latency Time Toward Thermal Stimulus on day- (sec ± SEM)					% Decreasing of Latency Time on day-7
	0	1	3	5	7	
Sham (n = 4)	7.62±0.60	6.22±0.66	4.92±0.26	6.18±0.26	6.98±0.22	8.40
PSNL (n = 20)	8.76±0.29	5.11±0.33*	3.94±0.18*	3.32±0.15*	3.13±0.20*	64.27

Data were presented as mean (SEM), *p<0.05 means significant different compared to sham group using independent t-test.

Table 5: Increasing of latency time toward thermal stimulus after red ginger oil administration on day 10 and 14 after cfa-induced chronic pain

Group	Treatment	Increasing of Latency Time (%) Day-	
		10	14
Sham (n=4)	Saline	-2.75	2.97
	Saline	-42.76	-44.54
CFA (n=20)	RGO 100 mg/kg	-15.20	-5.22
	RGO 200 mg/kg	-25.53	-9.14
	RGO 400 mg/kg	-10.21	10.37
	RGO 600 mg/kg	-9.14	4.63

RGO: Red ginger oil

of mice significantly increased (p<0.05) compared to CFA group, but still significantly lower than sham group (p<0.05). At the end of treatment (day-7), red ginger oil dose 100, 200, 400 and 600 mg/kgBW had the latency time toward thermal stimulus as same as sham group. On the other hand, the paw thickness of treatment group after seven days were significantly decreased (p<0.05) compared to CFA group, but still significantly bigger (p<0.05) than sham group as shown as fig. 2.

Red Ginger Oil Activity in PSNL-induced Neuropathy Pain

Red ginger oil administration dose 100 mg/kgBW, 200 mg/kgBW, 400 mg/kgBW and 600 mg/kgBW for 7 days changed the hyperalgesia response in mice. The latency time toward thermal stimulus continuously improved with longer duration of treatment. The increasing of the dose also gave significant improvement of the latency time toward thermal stimulus, as well. At day-12 and 14 (5 and 7 days after treatment), red ginger oil administration in all

Table 6: Increasing of latency time toward thermal stimulus after red ginger oil administration on day 10 and 14 after psnl-induced chronic pain

Group	Treatment	Increasing of Latency Time (%) Day-	
		10	14
Sham (n=4)	Saline	18.19	30.08
PSNL (n=20)	Saline	-38.10	-40.54
	RGO 100 mg/kg	-13.32	23.21
	RGO 200 mg/kg	7.45	46.85
	RGO 400 mg/kg	-8.31	26.36
	RGO 600 mg/kg	-0.43	32.09

RGO: Red ginger oil

Table 7: The Essential Oil Composition of Red Ginger Oil

Peak	RT	% Area	% Height	Name
1	3.987	5.24	5.85	Alpha-pinene (-)-
2	5.013	14.55	14.09	Camphene
3	5.788	2.81	6.78	beta-Myrcene
4	7.108	2.54	3.75	Cyclohexene,1-methyl-4-(1-methylethenyl)-
5	7.259	1.10	4.26	Cyclohexene,1-methyl-4-(1-methylethenyl)-
6	7.442	1.33	3.11	beta-Phellandrene
7	7.568	1.20	3.65	Sabinene
8	8.141	8.99	11.48	1,8-Cineole
9	9.395	0.71	2.57	alpha-Terpinolene
10	10.301	0.68	3.16	Linalool
11	10.492	1.68	2.54	3-Methyl-2-(2-methyl-2-butenyl)-furan
12	10.942	0.62	1.44	trans-3(10)-Caren-2-ol
13	11.417	0.59	0.48	Bicyclo(2.2.1)heptan-2-ol, 1,5,5-trimethyl-(C)
14	12.831	1.52	1.23	Citronella
15	13.908	13.04	7.27	endo-Borneol
16	14.317	5.08	5.70	3-Cyclohexene-1-methanol, alpha.,alpha.,tr
17	14.748	4.93	3.70	beta-Citronellol
18	15.467	0.94	2.90	Z-Citral

doses had latency time toward thermal stimulus as same as sham group. Even if red ginger oil dose 200 mg/kgBW had latency time toward thermal stimulus, but it did not significantly different compared to sham group as seen as table 6.

GC/MS analysis for red ginger oil

The composition of essential oil of red ginger was analyzed by GC/MS. There were 19 compound identified with the library, as shown in fig. 4 and table 7. From the result, champene was the highest compound in red ginger oil, followed by 1,8-cineole.

DISCUSSION

Chronic pain can be caused by chronic inflammation and neuropathy. In this research, we used two models to induce chronic pain. For inflammatory model, CFA that is consisted of inactivated and dried mycobacteria, used as inducer for chronic inflammation. CFA is effective in stimulating cell-mediated immunity and leads to

potentiation of T-helper cells that stimulates production of certain immunoglobulin and effect or T-cells (Anfenan, 2014; Calder, 2006). This process initiates inflammatory pain and responsible for the increasing of latency time toward thermal stimulus and paw thickness, compared with baseline (before induction). On the other side, for neuropathy model, we used PSNL method. The advantages of PSNL are because this method is analog to neuropathy in human that caused 60% of hyperalgesia and allodynia (Bridges *et al.*, 2001; Xie, 2011). That statement was consistent with our result, that PSNL induced hyperalgesia by 64.27%.

Chronic inflammation and neuropathy caused imbalance between the composition of inhibitory and excitatory neurotransmitter in central nervous system (CNS). Influx of oxidative stress in chronic pain increases the release of glutamate as excitatory neurotransmitter that bonds to N-Methyl-D-Aspartate (NMDA) receptor, caused depolarization and activation of central pathway. Long-term depolarization causes losing of magnesium

inhibitory in NMDA channel, affects calcium entry to intracellular and activated NMDA receptor NR2B subunit. This pathway is the key of chronic pain pathophysiology (Macintyre *et al.*, 2010; Zhu *et al.*, 2011).

After treatment using red ginger oil, there was an improvement in pain behavior of mice with chronic inflammation and PSNL-induced chronic pain. But, the effective dose that was needed to reduce pain was slightly different. In CFA-induced inflammatory pain, red ginger oil dose 400mg/kgBW was the most effective dose to minimize the hyperalgesia by increasing of latency time toward thermal stimulus 10.37%. Meanwhile, in PSNL-induced neuropathy pain, red ginger oil dose 200 mg/kgBW had the best antihyperalgesia activity by increasing of latency time toward thermal stimulus 46.85%, higher than in inflammatory pain. Even though the administration of red ginger oil could reduce hyperalgesia in CFA-induced inflammatory pain condition, but the paw thickness of mice still not returned yet to its baseline. It might be because of the lower ability to reduce hyperalgesia, just 10.37%.

The activity of red ginger oil was based on the composition of essential oil. Sivasothy *et al* (2011) found that red ginger oil was consisted by monoterpene, with camphene (14.5%), geranial (14.3%) and geranyl acetate (13.7%). From our GC/MS analysis, the biggest component of red ginger oil was camphene, that one of the monoterpene compound.

The latest studies showed that monoterpenoid had antinociceptive and anti-inflammatory activity (Hernani, 2011; Kumari *et al.*, 2014). Other research also found that this compound had antioxidant effect through reducing of oxidative stress in pathophysiology of chronic pain (Janes *et al.*, 2011; Quintans-Junior *et al.*, 2013). One of the mechanisms of how oxidative stress-induced sensitization in chronic pain is by causing loss of gamma-amino butyric acid (GABA) neuron. Antioxidant treatment showed increasing of GABA activity then rebalanced neurotransmitter in CNS and reduced chronic pain (Yowtak *et al.*, 2013). Red ginger oil action was related to induction of GABA's action (Choi *et al.*, 2017). The availability of GABA restored the balancing between excitatory and inhibitory neurotransmitter in CNS (Chandra *et al.*, 2005). GABA suppresses the release of glutamate and blocks calcium intake into intracellular. This condition decreases NR2B activity and pain sensitization.

The other mechanism of red ginger oil is probably related to decreasing of pro-inflammatory mediator such as prostaglandin that is produced via biosynthetic of cyclooxygenase. When this way is blocked, the production of prostaglandin will decrease and reduces the

inflammation (Nogueira *et al.*, 2011; Vendruscolo *et al.*, 2006). Even if red ginger oil could reduce the paw thickness by this pathway, but the thickness paw of mice with CFA-induced inflammation not returned yet to baseline. It might be because there were complex mechanisms in chronic inflammation that involved the immunity system.

CONCLUSION

Red ginger oil has antihyperalgesia activity in mice with chronic pain that are induced by inflammation and neuropathy by prolong the latency time toward thermal stimulus. Camphene, the highest compound in red ginger oil, is believed responsible for this action. Based on this research, red ginger oil have an opportunity to be developed further to be antihyperalgesia.

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