

Original Article

ANTIEMETIC ACTIVITIES OF INDONESIAN STINGLESS BEE PROPOLIS ON EMETIC INDUCED BY ANTI-TUBERCULOSIS DRUGS

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ABSTRACT

Objective: This study aims to determine the antiemetic potential of stingless bee propolis in reducing the prevalence of nausea due to consumption of Anti-Tuberculosis Drugs (ATD) in Tuberculosis patients and to identify phytochemical compounds that act as an antiemetic in propolis.

Methods: The stingless bee propolis used was *Wallacetrigona incisa* from South Sulawesi. The clinical testing used the randomized controlled trial, randomization using permuted block randomization consisting of one positive control group and two treatment groups. The active components analyzed using Gas Chromatography-Mass Spectrometer (GC-MS) pyrolyzer.

Results: This study found that the measurement at week 0 obtained the mean value of nausea per week for each group P0 (Placebo), P1 (Propolis 6%), and P2 (Propolis 30%) were respectively 2.14; 1.5 and 5.2 events/week, at week 8 the prevalence of nausea by 2.0; 1.0; and 1.6 events/week, and week 24 the prevalence of nausea by 3.0; 0; and 0 events/week. There are 11 compounds with concentrations above 1% that act as antiemetic compounds either through direct and indirect mechanism with a total concentration reaches 75,47%.

Conclusion: Based on all determinant parameters, propolis of *Wallacetrigona incisa* species from South Sulawesi has antiemetic activity and can reduce the prevalence of emetic induced by ATD consumption in pulmonary TB patients.

Keywords: Antiemetic, Antiemetic Compounds, Anti-Tuberculosis Drug, Stingless Bee Propolis, Nausea

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INTRODUCTION

Pulmonary tuberculosis (TB) is an infectious pulmonary disease that is still prevalent in Indonesia. In 2018, 570.289 pulmonary TB cases were recorded and treated in Indonesia, with an estimated mortality index of 12% [1]. Infection of pulmonary TB is caused by *Mycobacterium tuberculosis* (MTB), is a pathogenic bacteria that can live and multiply inside and outside phagocytic cells so that the process of forming a bacterial colony is difficult to control and resist [2].

TB control in Indonesia started in 2000 by implementing the DOTS (*Directly Observed Treatment Short-course*) strategy. This strategy is a treatment step using anti-TB drugs (ATD), which consists of a combination of several types of drugs that are effective in treating TB [3]. Combining ATD is considered effective but has side effects, such as nausea, vomiting, and appetite loss [4]. The effects will decrease a patient's nutritional intake and worsen the patient's nutritional status, which causes a longer recovery process [5]. The condition of nausea and vomiting can be minimized by administering an antiemetic compound (anti-nausea) and one of the products proven to have antiemetic properties is propolis [6, 7].

Propolis is a resin that is produced by bees and used as a hives building material. Propolis is formed from plant origin collected and processed by bees with the addition of various natural enzymes and saliva in their bodies [8]. Stingless bees produce propolis as a form of self-defense so that it produces more propolis than other species. Stingless bees propolis also has a high flavonoid content which made bees of this species more widely cultivated as propolis producers [9, 10]. Phytochemical compounds in the form of flavonoids and phenolics in propolis can play an active role as antioxidants, antimicrobials, antiseptics, and antiemetic [6, 11, 12].

The study on the benefits of propolis as antiemetic is still minimal, but Fikri *et al.* [6] conducted an antiemetic test of Indonesian propolis on chicks given CuSO₄ and reported that Indonesian

propolis reduced symptoms of nausea and has a similar effect with antiemetic power of metoclopramide (an anti-nausea drug). Induction of CuSO₄ in chicks will stimulate the irritated stomach wall that causes nausea and vomiting mechanisms. These mechanisms also occur in humans so that they are suitable for modeling the potential antiemetic of a compound or product [13]. The finding triggered to develop propolis as an antiemetic for humans, Sulaeman *et al.*, which states that propolis has the potential to reduce nausea and vomiting in pregnancy [11]. Therefore, this study is important to determine the antiemetic potential of stingless bee propolis in reducing the prevalence of nausea due to consumption of ATD in TB patients and to identify phytochemical compounds antiemetic in propolis.

MATERIALS AND METHODS

Materials

The material used in this study was propolis originating from South Sulawesi in stingless bees *Wallacetrigona incisa* which was harvested by a group of farmers and obtained through the intermediary CV. Nutrima Sehatalami, Bogor. The use of these samples is based on the active compound, IC50, and the propolis's toxicity has the best cumulative index value among other propolis in Indonesia [11, 12].

Propolis extraction

The method of extraction propolis was from patent no. P00201100811 in 2011 about short, productive, and efficient extraction method in the production of liquid propolis.

First, 1 kg raw propolis (still in the glass transition process) was cut to a smaller size, then mixed with 70% ethanol with a ratio 1: 2,5 (propolis: ethanol). This process was carried out at room temperature to avoid damage to propolis due to high temperatures. Then, propolis was mashed into propolis pulp and filtered using a

30-mesh filter before being left for 12 h. The filtrate was separated while the rest of the propolis pulp was mixed with ethanol 70% at a ratio of 1: 1,5 (propolis: ethanol) and was mixing for 5 min.

The next step was the evaporation of filtrate using a rotary vacuum evaporator connected to a vacuum pump with a pressure 4 kPa, rotation pump 3 rpm, at 50 °C. When the ethanol had evaporated out, the filtrate colours turned into light-brown and turned into dark-brown until the remaining water had evaporated. The result of this filtrate was a dark-brown extract of propolis. After that, the propolis extract was added with propylene glycol and was filtered using Whatman paper no. 50.

Clinical testing

The design used was a randomized controlled trial, randomization using permuted block randomization [14], consisting of one positive control group and two treatment groups. Intervention and testing were carried out in a double-blind manner (both the investigator and the subjects were unaware of the treatment given). The subject size was determined according to the sample size table in a controlled clinical trial [15]. Based on the table, assuming a significance level of α 0.05 and a power of 80%, the minimum sample size is 13 subjects per group. The samples used 50 subjects to ensure data security and validity.

The criteria for the research subjects were as follows: a) Inclusion criteria: TB patients, aged 12-45 y (adolescents-adults), willing to participate in the study by signing informed consent; b) Exclusion criteria: smoking, suffering from hepatitis or other diseases that interfere with the study, drinking alcohol, pregnant, breastfeeding, using contraceptives, taking other drugs or herbs or supplements, and TB patients recurring.

The propolis dose in the subject was carried out with an approach as a companion drug for ATD. The positive control group was given a companion in the form of propylene glycol liquid placebo. The dose determination of treatment group one was based on the clinical dose of Pranandaru *et al.* (2011), were 3 drops of propolis (20% concentration) in TB patients, the dose given for group one was twice from the reference dose by administering 20 drops of propolis (6% concentration) [16]. The dose given for group two was 30 drops of propolis (30% concentration), was equivalent to five times the dose for group one and was still lower than the clinical dose of Liu *et al.* (2013), 103,2 drops of propolis. This method used an equalization of the number of propolis droplets of 20 drops in one use; one drop of propolis was equivalent to 0,028 ml assuming a 6 ml volume eye drop bottle (20 drops \approx 0.56 ml) [17]. The propolis had given every day for 56 d (2 mo early in the intensive phase of pulmonary TB treatment with ATD, then follow-up control was

carried out of given propolis 3 times a week for 16 w (the next stage of pulmonary TB treatment with ATD).

The incidence of nausea was observed for 6 mo with data retrieval 3 times, namely during the first week of initial intervention (W0), the intensive transition period to the advanced stage (W8), and the last week of intervention (W24).

All clinical experiments were carried out under ethical approval from the Health Research Ethics Committee, Faculty of Medicine of University of Indonesia number: 1036/UN2.F1/ETIK/2015.

GCMS (Gas Chromatography Mass Spectrometry) analysis

This study used Shimadzu GCMS-QP 2010 with *pyrolysis*, with the carrier gas is in the form of Helium UHP, rt x 5 ms column. The column oven temperature was set to 50 °C for 5 min, then gradually increase to 280 °C. The temperature injection pressure was set at 101 kPa with column flow 0,85 ml/min. MS detector was set at ion source temperature (200 °C), interface temperature 280 °C, detector temperature 280 °C, pyrolyzer temperature 300 °C. When stable, 1 μ g/1 drop liquid propolis was injected into the pyrolyzer, and GC-MS worked automatically. The process of determination took 50 min, and the results of chromatogram were stored on a computer. The active compounds of propolis were identified using the Willey standard and Nist Libraries on GCMS data system.

Phytochemical screening

Phytochemical screening was to examine the active compounds of propolis which acts as antiemetic. The chromatogram from the GC-MS *pyrolysis* results contains information about active compounds of propolis sample. Furthermore, a literature study was carried out to find the biological activity or mechanism of each active compound's action, from *in vitro*, *in vivo*, and clinical research. The GC-MS chromatogram was compared to literature studies to find every active compound of propolis that could reduce the prevalence of nausea during ATD consumption.

RESULTS AND DISCUSSION

Effects of propolis on the prevalence of nausea

Nausea is a symptom that can be used as an indication or response to the presence of toxic compounds that enter the body [18, 19]. The sensation of nausea can be suppressed or eliminated through phytochemical compounds with antiemetic activity [13]. As an ATD companion, performed to reduce nausea and vomiting symptoms due to side effects of pulmonary TB treatment using ATD. The results of the measurement of the average prevalence of nausea are presented in fig. 1.

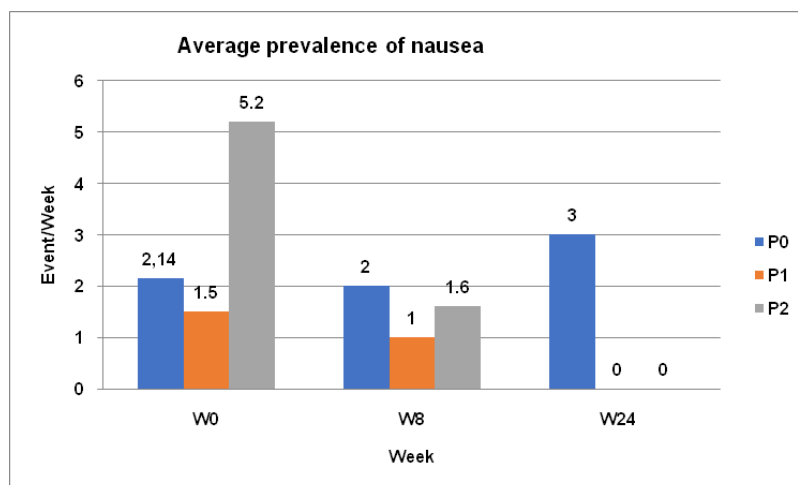


Fig. 1: Changes in average prevalence of nausea

Based on the results of the graph in fig. 1., the measurement at week 0 obtained the mean value of nausea per week for each group P0, P1,

and P2 were respectively 2.14; 1.5 and 5.2 events/week. Variation of data on P2 value has the highest number compared to other groups,

the difference in data is considered normal. The grouping of research subjects has been carried out evenly by using *permuted block randomization* methods based on the sex and age of the patient so that the response that appears has a low level of bias for confounding variables [15, 20].

Measurement of the 8th week of all treatment groups decreased the prevalence of nausea by 0.14; 0.5; and 3.6 events/week for groups P0, P1 and P2. Based on these data, the P2 group until the end of the intervention (propolis supplementation), namely at week 24th showed the greatest decrease until it reached a value of 0 incidents of nausea/week, followed by group P1, which also experienced a decrease to a value of 0 incidents of nausea/week, while the group P0 has increased the prevalence of nausea/week.

The increase in the prevalence of nausea in the P0 group is an indication of the presence of toxic compounds from ATD that accumulate in the digestive tract, plasma, and even *Cerebrospinal fluid* (CSF) [18, 19, 21]. These toxic compounds come from the consumption of ATD, first-line ATD (Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol) are cytotoxic drugs; these properties are needed to destroy MTB cell [22, 23]. Its presence in the body as a toxic compound often causes side effects such as nausea, vomiting, indigestion, and others [22, 24].

This can be severe due to allegations of liver injury resulting from the consumption of hepatotoxic ATD [25]. Consumption of ATD for a long time will cause the accumulation of toxic compounds resulting in chronic toxicity conditions and lead to liver injury [21]. Liver injury will have an impact on the reduction of liver function as a detoxifying organ and will cause symptoms of nausea and vomiting if exposed to toxic compounds and accumulation of toxic compounds [19, 21, 26, 27]. Isoniazid, rifampicin and pyrazinamide are hepatotoxic drugs, the metabolism of these compounds is carried out in the liver with the help of the body's natural enzymes [22].

Isoniazid is the most toxic drug in the first-line ATD, because isoniazid is a toxic compound both from its function as a radical compound that destroy Tb cells and in terms of its intermediate metabolites which are more toxic and capable of damaging liver cells [22, 24, 26]. Rifampicin is a toxic compound that is easily detoxified by the liver, but when combined with isoniazid, rifampicin will cause an increase in the level of toxicity to the liver [22, 23, 26]. Meanwhile, pyrazinamide is the most hepatotoxic drug because of its use, it causes more symptoms of liver damage than other drugs, and it is even recommended to be replaced by a combination of first-line ATD [28].

The phenomenon of increasing the prevalence of nausea caused by liver damage has attracted the attention of researchers because apart from having antiemetic activity, Indonesian propolis also function as a hepatoprotector. The active compounds in propolis are able to protect the liver from the toxic effects of ATD [11, 29]. Therefore, liver damage can be anticipated, so that the function of the liver as a detoxification organ is not disturbed and the incidence of emesis can decrease.

The final results of the observation group P1 and P2 experienced a decrease when compared to before the intervention, the value of the decrease was 1.5 and 5.2 incidents of the nausea/week, while the P0 group experienced an increase of 0.86 incidents of the nausea/week. Thus, the P2 group experienced the greatest decrease in the prevalence of nausea and vice versa, the P0 group experienced an increase in the prevalence of nausea. This shows that the treatment of propolis supplementation with a concentration of 6% (P1) and 30% (P2) against TB patients who consume ATD has an antiemetic effect.

Antiemetic compounds propolis *wallacetrigona incisa* from south sulawesi

Identification of the active compound of ATD complementary propolis was carried out using the *GCMS pyrolysis* and found about 100 constituent compounds. These compounds are phytochemical compounds which are derivatives of polysaccharide compounds, lipopolysaccharides and amino polysaccharides. The identification of active antiemetic compounds will only be carried out on compounds with concentrations above 1%, with the consideration that the consumption of propolis as a complement to ATD is only 20 drops

(equivalent to 0.56 ml) so that the concentration is considered too low. In addition, compounds with a concentration of <1% have not much known biological activity, although there is a possibility that they may have a direct antiemetic activity or a synergistic relationship with other compounds.

There are 16 compounds with concentrations above 1% with a total concentration of 84.46%. The list of active compounds along with their concentrations and biological activities, are shown in detail in table 1. The function of these compounds has been further identified, especially their role as antiemetic by the literature study method. The functions of these compounds were investigated, especially as an anti-emetic by means of literature studies. Based on the results of the literature study, it was found that 16 compounds had a concentration of >1%, and as many as 11 compounds had antiemetic activity either directly or indirectly, 1 compound had biological activity other than antiemetic and 3 compounds had no biological activity. Compounds that have antiemetic activity include: (1) *Methyl- α -D-glucopyranoside*, (2) *5-Azulenemethanol, 1,2,3,3a, 4,5,6,7-octahydro-alpha. alpha, 3, 8-tetramethyl*, (3) *1,2,3-Propanetriol*, (4) *Hexadecanoic acid*, (5) *Ethyl Ester 3-Hydroxy-Tridecanoic Acid*, (6) *2,6-Dimethoxyphenol*, (7) *Pentadecanoic acid, 14-methyl-, methyl ester*, (8) *1,6-Anhydro-Beta-D-Glucopyranose*, (9) *(2S, 3R)-3-Allyl-3-methylapfelsaure-4-ethylester*, (10) *1,4, 5-Trimethylnaphthalene*, (11) *Tetradecanoic acid*. Compounds that have biological activity are: *Isosorbide*. Meanwhile, 3 compounds that have not been found with biological activity are: (1) *2-Methoxyethyl acetate*, (2) *8-Oxabicyclo [5.1.0] octane*, (3) *Dimethyl 2-hydroxy-2-methylbutane-1,4-dioate*.

The remaining 86 compounds had a concentration of <1% with an accumulated concentration of 15.54%. The amount of accumulated compound concentration <1% causes the combination of compounds that might have the potential for antiemetic activity both in single compound function or in synergy interaction between compounds in propolis or in the body. The role of these compounds needs to be studied further because it can have an impact on the response to the prevalence of nausea. However, this study did not discuss each of these compounds due to the low concentration of each compound, which would raise questions about the benefits of significant and effective dosages.

Based on literature studies, propolis of *Wallacetrigona incisa* from South Sulawesi have antiemetic activity through two mechanisms: (1) Direct antiemetic mechanism in the form of compounds that are inhibitors of 5-HT4 stimuli, (2) Indirect antiemetic mechanism by inducing compounds in the body that capable of suppressing emetic.

The direct antiemetic mechanism is based on the research of Eda et al. [7] stated that it was found that the antiemetic activity of propolis was caused by *terpenoid* and *flavonoid* group compounds. In propolis *Wallacetrigona incisa* from South Sulawesi was found 2 compounds belong to the group of compounds, namely: *5-Azulenemethanol, 1,2,3,3a, 4,5,6,7-octahydro-alpha. alpha, 3,8-tetramethyl (terpenoids)*, and *Methyl- α -D-glucopyranoside (flavonoids)*. Both compounds have a total concentration of 38.35% (36.13+2.22).

5-Azulenemethanol, 1,2,3,3a, 4,5,6,7-octahydro-alpha. alpha, 3,8-tetramethyl compound or better known as *bulnesol* compound which is a *terpenoid* group of *sesquiterpene* types founded in seasonings, spices and essential oils from tree wood, especially of *ferula* species. *Bulnesol* is strongly thought to provide a protective effect on the stomach and reduce gastrointestinal hyperactivity. This assumption is based on the research of Eda et al. [7] who found the use of terpenoid compounds in Brazilian propolis extracts that we're able to reduce retching in chicks given nausea agents. According to Ahmed et al. [13] the induction nausea agents in chicks can trigger emesis through the stimulus of the stomach wall through stimulation of 5-HT4, a natural compound *terpenoid* such as *sesquiterpenes* and *triterpenes* are thought to be able to inhibit 5-HT4 stimuli. This mechanism is one of the mechanisms that also causes nausea and vomiting in humans. Apart from having a similar mechanism, this model is also suitable for evaluating the involvement of the brain in the emergence of emetic [37]. Another function of *bulnesol* along with their isomeric components, namely *guaial* has biological activity as an antimicrobial compound [38], and

antifungal [39]. *Bulnesol* is also found in Lebanese Propolis and

Chinese Propolis [40, 41].

Table 1: Active compounds of propolis *W. Incisa* detected using GCMS Pyrolysis

No.	Compound name	RT	Concentration (%)	Antiemetic activity	Type of mechanism
1	2-Methoxyethyl acetate	8,510	1,16	-	-
2	8-Oxabicyclo[5.1.0]octane atau Epoxyoctane	12,942	2,16	-	-
3	1,2,3-Propanetriol (gliserol)	13,396	6,45	[30, 31]	2
4	Isosorbide	15,129	1,5	-	-
5	Ethyl Ester 3-Hydroxy-Tridecanoic Acid (C13)	16,333	2,06	[14]	3
6	2,6-Dimethoxyphenol	16,392	1,67	[32]	3
7	Methyl- α -D-glucopyranoside (flavonoid)	16,741	1,33	[7]	1, 3
8	1,6-Anhydro-Beta-D-Glucopyranose (Levoglucofan)	18,166	4,44	[33]	3
9	(2S,3R)-3-Allyl-3-methylpiperidone-4-ethyl ester (allicin)	18,436	2,50	[34, 35]	3
10	5-Azulenemethanol, 1,2,3,3a,4,5,6,7-octahydro- α , α , 3,8-tetramethyl (Sesquiterpen)	18,517	2,22	[7]	1, 3
11	1,4,5-Trimethylnaphthalene	18,625	1,83	[36]	3
12	Methyl. α -D-glucopyranoside (flavonoid)	19,158	34,80	[7]	1, 3
13	Dimethyl 2-hydroxy-2-methylbutane-1,4-dioate	19,442	4,17	-	-
14	Tetradecanoic acid (Miristic acid; C14)	19,542	13,92	[14]	3
15	Pentadecanoic acid, 14-methyl-, methyl ester	20,343	3,02	[14]	3
16	Hexadecanoic acid	20,908	1,23	[14]	3
Total Concentration of Antiemetic Compound			75,47		

Details: 1) 5-HT₄ stimulus inhibition 2) induction of glycerol kinase 3) hepatoprotector

Methyl- α -D-glucopyranoside is a sugar/glucoside compound that belongs to the flavonoid group. Among all the active compounds detected by GC-MS pyrolysis, this glucoside compound is the main component of *Wallacetrigona incisa* propolis because it has the highest concentration of 36.13% (1.33%+34.80%). As the main component, *Methyl- α -D-glucopyranoside* has various biological activities: anti-tuberculosis [42], antibacterial [43], antifungal [44], antitumor [45], antivirals [46], and antiemetic [7]. Glycosides are strongly thought to have a protective effect on the stomach and reduce gastrointestinal hyperactivity. This assumption is based on the research of Eda et al. [7], which found flavonoid in the Brazilian propolis extract that was able to reduce retching in chicks given nausea agents. Due to its high concentration and various biological activities, the presence of *Methyl- α -D-glucopyranoside* as the main composition of propolis is able to make propolis as a nutritional companion of ATD, which is effective in suppressing symptoms of emesis and in the treatment of pulmonary TB.

The indirect antiemetic mechanism is based on the identification of compounds capable of inducing other compounds in the body, the compounds that are induced have a function in reducing and even eliminating the incidence of emetic. Based on this, there are two mechanisms that can occur, the mechanism for the formation of the enzyme glycerol kinase and the hepatoprotective. The mechanism for the formation of the glycerol kinase enzyme as a compound to prevent nausea and vomiting is carried out by glycerol compounds [30, 47], while the hepatoprotective mechanism is carried out by compounds that have antioxidants and anti-inflammatory activity [48, 49].

1,2,3-Propanetriol or glycerol is a glyceride compound that makes up various fatty acids. The concentration of glycerol in propolis *Wallacetrigona incisa* from South Sulawesi based on GC-MS pyrolysis was 6.45%. Glycerol is able to prevent nausea and vomiting indirectly by inducing the formation of the enzyme glycerol kinase in the body. The activity and the amount of the glycerol kinase enzyme in the body is strongly influenced by the amount of ATP and glycerol available in the body; the relationship is a positive correlation [50]. The presence of glycerol and glycerol kinase in the body plays a role in the gluconeogenesis metabolic pathway in the liver, which will produce glucose [31]. This process occurs when the body is deficient in glucose, glycerol kinase will carry out a phosphorylation reaction against glycerol with a source of phosphate originating from ATP to form glucose-forming intermediates [31, 50]. According to Johnston et al. [51], the absorption of glycerol and the process of gluconeogenesis can be inhibited if there is damage to the liver. Thus, the hepatotoxicity caused by the consumption of ATD will cause a decrease in glycerol

absorption and a decrease in the amount of the enzyme glycerol kinase. Deficiency of the enzyme glycerol kinase can cause nausea and vomiting symptoms [30, 31, 47].

Prevention of nausea and vomiting can be done through a hepatoprotective mechanism. The hepatoprotector in the liver will prevent deficiencies in liver function as a detox and metabolic organ and prevent depletion of important enzymes such as cytochrome P450 [11]. By maintaining the liver, the symptoms of emetic caused by liver injury and the present of toxic compounds in the body can be minimized. The hepatoprotective mechanism is generally carried out through protective measures by phytochemical compounds that have antioxidant and anti-inflammatory activity [9, 49]. Antioxidant compounds will protect the liver from radical and toxic compounds produced by ATD such as ROS, *n*-hydrazine, acetylisoniazid and isonicotinic acid [22].

2,6-dimethoxyphenol [32], 1,6-anhydro-beta-d-glucopyranose [33], (2S, 3R)-3-Allyl-3-methylpiperidone-4-ethyl ester [34, 35], 1,4,5-trimethylnaphthalene [36] are tested to act as antioxidant and showed a reduction of radical compounds 2,2-diphenyl-1-picrylhydrazyl (DPPH). These compounds are able to reduce radical metabolites by binding to them by donating electrons.

Lipid group compounds such as tridecanoic acid, tetradecanoic acid, pentadecanoic acid and hexadecanoic acid in propolis also have active functions that act as antioxidants. According to Zheng et al. the four fatty acids have the ability to reduce radical 2,2-diphenyl-1-picrylhydrazyl (DPPH). The total concentration of compounds that act as hepatoprotectors (antioxidants) is 30.67% [14].

The compound methyl- α -D-glucopyranoside and 5-azulenemethanol, 1,2,3,3a, 4,5,6,7-octahydro- α , α , 3,8-tetramethyl, in addition to acting as antiemetics compound directly, both compounds also function as antioxidants and can act as hepatoprotectors by reducing radical metabolites [11, 52]. This is supported by the results of research by Kokanova-Nedialkova et al. [53] and Vinholes et al. [54] which showed that these two compounds had a strong ability to reduce radical 2,2-diphenyl-1-picrylhydrazyl (DPPH).

Based on the concentration and mechanism of compounds that act as antiemetic, the percentage of antiemetic compounds either through direct and indirect mechanisms reaches 75.47% (38.35%+6.45%+30.67%). This concentration is very large, even reaching 3/4 of the total concentration of propolis. Based on the concentration of these antiemetic compounds, the propolis of *Wallacetrigona incisa* from South Sulawesi is very potential as an

antiemetic product, supported by the effect of propolis in reducing the prevalence of emetic induced by ATD in pulmonary TB patients.

CONCLUSION

Propolis of *Wallacetrigona incisa* species from South Sulawesi has antiemetic activity and is able to reduce the prevalence of emetic induced by ATD consumption in pulmonary TB patients. Propolis concentration 30% showed better antiemetic activity than propolis concentration 6%. There are antiemetic compounds with a total concentration of 75.47%. The antiemetic mechanism occurs through three mechanisms: (1) Direct antiemetic mechanism in the form of inhibition of the 5-HT₄ stimulus which can trigger nausea and vomiting, (2) Indirect antiemetic mechanism by inducing the formation of the glycerol kinase enzyme which can suppress nausea and vomiting, (3) Indirect antiemetic mechanism by protecting the liver as a detoxifying organ for toxic compounds so that nausea can be avoided.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare no conflict of interest associated with this study.

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