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Research Article

Composition of Functional Drinks Based on Cardamom Rhizomes (*Amomum cardamomum* Willd.) and the Benefits as an Anti-inflammatory with an Improved Lipid Profile

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Abstract

Background and Objective: Various medications are available to treat inflammatory diseases, but these medications often have negative effects. This study was aimed at learning the composition of functional drinks based on cardamom rhizome (Fd-Carrhi) and the effect on the inflammatory and lipid profile of atherosclerotic women. **Materials and Methods:** The drink was made of 5 formulas with varying amounts of cardamom rhizome coupled with spices and boiled in water so that the liquid remained at 30-35%. A total of 55 untrained people tested the colours, flavours, aroma, spiciness, aftertaste and warm sensations, on a 5-point hedonic scale, ranging from extremely dislike to extremely like. Thirty atherosclerotic women, 40-65 years of age, hypertension, hypercholesterolaemia, hypertriglyceridemic and obese served as subjects and all took simvastatin. They were divided into 3 groups of 10 each: Group I was given Fd-Carrhi; Group II was given a placebo and group III was given only simvastatin for 2 months. Blood plasma was determined at the levels of IL-6, C-RP, total cholesterol (Tc), triglyceride (TG), LDL-c and HDL-c. **Results:** Fd-Carrhi was composed of 18% cardamom rhizomes, 9% wood secang, 3.6% cinnamon, 0.3% cloves, 3.6% flower mace, 45% ginger, 13.7% lemongrass, 2.6% low calorie sugar, 0.5% salt and 3.7% lime leaves. Compared to the placebo, Fd-Carrhi significantly reduced plasma IL-6, C-RP, total cholesterol and LDL-c and increased HDL-c, but no differences were observed in TG. **Conclusion:** Fd-Carrhi inhibits the development of atherosclerosis towards cardiovascular heart diseases.

Key words: Cardamom-rhizome, composition, functional drinks, anti-inflammatory, anti-cholesterolemic, phenolic, vitamin C

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Inflammation is one of the factors that induce atherosclerosis. Clinical studies have determined that inflammation status is reflected on the high level of hs-CRP and IL-6 in plasma[1,2]. High levels of cytokine have been reported to contribute to the early stages of coronary artery disease[3]. The hs-CRP is the result of hepatic inflammation and is managed by cytokine IL-6, while messenger pro-inflammatory cytokines are secreted by macrophages and smooth muscle cells in atherosclerotic lesions. Therefore, hs-CRP and IL-6 can be used to predict the development of atherosclerosis towards Cardiovascular Disease (CVD)[4]. Kumar *et al.*[5] reported that CVD is more prevalent in women than in men. High markers for inflammation are related to the increasing risk of atherosclerosis. Accordingly, Frostegard[6] ensured that anti-inflammatory treatment is considered the new medication for CVD.

Hypercholesterolaemia is also related to atherosclerosis. LDL-c transports cholesterol from the liver into the tissues for body performance, while HDL-c transports cholesterol from the tissues to the liver. However, when the LDL-c level is higher than normal, LDL-c can accumulate in the artery and increase the risk of plaque that clogs the artery, a condition called atherosclerosis. In atherosclerotic lesions, a more electronegative LDL-c than native LDL-c is found[7]. The contributing factor of atherogenesis is not native LDL but oxidized LDL (LDL-ox), while the formation of LDL-ox is the effect of a high level of LDL-c. Thus, it is crucial to minimize the level of either LDL-ox or LDL-c. Several studies have reported that the emergence of degenerative diseases is due to accumulation of free radicals in the body[8,9]. One substance that can control the work of free radicals is antioxidants.

Not many people know about cardamom rhizome (*Amomum cardamomum* willd.), let alone make it as a beverage. Winarsi *et al.*[10] stated that every part of the cardamom plant contains bioactive compounds, including 324.51 mg g^{-1} flavonoids, 0.73 mg g^{-1} vitamin C and 0.22 mL g^{-1} essential oil in that rhizome[11]. Flavonoids are potent antioxidant compounds that have anti-inflammatory[12] and vasodilation properties[13]. Winarsi *et al.*[11] added that the rhizome cardamom is proven to erode levels of LDL-ox and lower the total cholesterol in rat atherosclerosis, even improving antioxidant and immune status. However, a functional drink formula based on cardamom rhizome that can control inflammation and the lipid profile of atherosclerotic women has not been found. This study aimed to determine the composition of functional drinks based on cardamom rhizomes that can control inflammation and the lipid profile of atherosclerotic women.

MATERIALS AND METHODS

Current study used a randomized clinical trial with a double blind approach. The research was approved by the Ethics Committee of the Medical Faculty of Diponegoro University and Central General Hospital, Dr. Kariadi, Semarang, Indonesia, with No. 292/EC/FK.RSDK/V/2017, 30 May, 2017.

Preparation of the cardamom chip rhizomes and Fd-Carrhi: The cardamom rhizome was obtained from cardamom farmers in the village of Sumbang, Banyumas, Central Java, Indonesia. After washing, cardamom rhizomes were thinly sliced and then dried in a cabinet dryer at 57°C. Therefore, the water content was 4-6%. The sliced rhizomes were called cardamom chip rhizomes (CCRs)[14].

The drinks were composed of a variety of CCRs coupled with spices such as wooden cup, cinnamon, cloves, star anise, ginger, lemongrass and lime leaves, as well as low calorie sweetener and a little salt. Extra spices were to adopt the custom of the people in Jogyakarta City, Indonesia, who often drink "wedang uwuh," which contains an assortment of spices. In addition to cardamom seeds, cardamom rhizomes also have a spicy taste and a pleasant aroma and are slightly bitter and warm. Therefore, the addition of spices that aim to improve the taste and aroma is less likely to be acceptable to people. Many spices are added to formulations based on the findings of Winarsi *et al.*[15] Preparation of Fd-Carrhi begins with creating a formula for the five proportions of CCRs and spices presented in Table 1. The CCRs, wooden cup, cinnamon, cloves, star anise and crushed ginger and lemongrass were incorporated into 500 mL of water and brought to a boil. The heat was reduced while stirring occasionally until 30-35% of the liquid was left and then filtered. Lime leaves were added, the mixture was brought to a boil again, filtered and then, sweetener and a little salt were added. The product is here in after referred to as a cardamom rhizome-based drink (Fd-Carrhi).

Sensory evaluation of Fd-Carrhi: To determine the level of consumer acceptance, sensory properties (hedonic) of Fd-Carrhi were tested, including colours, flavours, aromas, spiciness, aftertaste and warm sensation. The hedonic test is one of the kind to test consumer acceptance of a product. A total of 55 untrained panelists were assigned to the study[16]. The panel members were asked to reveal their personal response as affection or dislike and then to raise the level of likes and dislikes with the hedonic scale. Attributes tested were colour, flavour, aroma, spiciness, aftertaste and warm sensation for 5 samples of formula drink (103, 306, 138, 602,

Table 1: Proportion of cardamom rhizome and spices

	Formula code				
Component (g)	103	306	138	602	901
CCRs	5.00	7.50	10.00	12.50	15.00
Wooden cup	5.00	5.00	5.00	5.00	5.00
Cinnamon	2.00	2.00	2.00	2.00	2.00
Cloves	0.14	0.14	0.14	0.14	0.14
Star anise	2.00	2.00	2.00	2.00	2.00
Ginger	25.00	25.00	25.00	25.00	25.00
Lemongrass	7.63	7.63	7.63	7.63	7.63
Low calorie sweetener	2.50	2.50	2.50	2.50	2.50
Lime leaves	2.00	2.00	2.00	2.00	2.00

CCRs: Cardamom chip rhizomes

901). A five-point hedonic scale was used, where 1 = Dislike extremely, 2 = Dislike moderately, 3 = Neutral, 4 = Like moderately and 5 = Like extremely. To verify the reception of the drinks tested and to standardize and evaluate each sensory attribute, the amount of acceptable factor (AF) was determined[17] based on the following Eq:

$$AF = A.\ 100.\ B^{-1}$$

Where:
A = Average value obtained for each attribute
B = Average maximum value for each attribute

Physicochemical characterization and proximate analysis of the selected Fd-Carrhi: Physicochemical characterization of the selected Fd-Carrhi included pH, level of total phenols and vitamin C. The proximate analysis included water, ash, protein, lipid and carbohydrate[18].

pH was measured using a pH meter model HI9321 (Hanna Instruments, Romania). Prior to the first measurement, the pH meter was standardized using standard buffers at pH 4 and 7. The electrode was rinsed with aquadest and dried with a paper tissue. The electrode was dipped into the sample solution and left until a stable reading was obtained and the pH value was recorded (SNI 01-2891-1992).

Determination of total phenol content of Fd-Carrhi selected used the Folin-Ciocalteu method. Tannic acid was used as a standard and the results obtained were expressed as mg/100 g or ppm[19].

Vitamin C was determined using iodine titration[20]. The sample weighing 25 mg was dissolved in 50 mL aquadest and 2 mL amylum 0.5% to perform titration with a solution of iodine (I2) and a blue colour appeared.

Selection, grouping and intervention of research subjects: Research subjects were 30 atherosclerotic women, 40-65 years old and suffering from hypertension (>140/90 mm Hg), hypercholesterolaemia (>200 mg dL^{-1}) and obesity (BMI>25 kg m^{-2}). The subjects lived in Purwokerto, Banyumas Regency, Central Java, Indonesia and were willing to sign the informed consent. Subjects were randomly assigned to three groups of 10 and took simvastatin from the doctor. Group I was given Fd-Carrhi, group II was given a placebo (Fd-Carrhi without CCRs) and group III was given only simvastatin. Intervention was performed in 2 months. Fd-Carrhi and placebo were given 100 mL/day one time a day via delivery to the subject's house every morning between 06.00 and 08.00 a.m. to be taken directly.

Blood samples were taken three times, 3 mL each on the baseline and then 1 and 2 months after intervention. The blood sample was taken using Venoject with 10% EDTA. Blood was centrifuged at 3,000 rpm for 10 min, the plasma was separated and then the IL-6, C-RP, total cholesterol, triglycerides, LDL-c and HDL-c were evaluated.

Statistical analysis: The result was expressed as the Mean±SD. The data obtained were subjected to one-way ANOVA followed by the Duncan test in cases of significance of 5% error.

RESULTS AND DISCUSSION

In this research, the CCRs scent was astringent, less savoury aroma and chelate.

Preparation of Fd-Carrhi refers to the cardamom leaf-based formula drink by Winarsi *et al.*[15] with slight modifications. To obtain a formulation that was acceptable and preferable by the panelists, 5 formulas for varied amounts of CCRs (Table 1) were prepared. Each formula was combined with 500 mL water and boiled for a certain time. The longer the boiling, the more viscous the liquid obtained. To obtain the desired viscosity, the heat was reduced after reaching the boiling temperature and then the mixture continued to simmer until approximately 30-35% liquid remained. Brownish and reddish liquid screening resulted and at first glance, no difference was apparent in the formula.

Table 2: Acceptance (average values ±SD) and acceptability factors (AF) for 5 formulas of Fd-Carrhi

Sensory characteristics	Sample code 103	306	138	602	901
Colour	2.85±0.99[b] (69.51)	3.00±0.92[b] (73.17)	4.10±0.85[a] (100)	2.90±0.91[b] (70.73)	3.15±0.99[b] (76.83)
Flavour	3.15±0.93[b] (72.41)	3.35±0.75[b] (77.01)	4.35±0.59[a] (100)	3.30±0.86[b] (75.86)	2.85±0.75[b] (65.52)
Aroma	3.40±0.82[b] (85.00)	3.65±0.81[a] (91.25)	4.00±0.65[a] (100)	3.65±0.89[a] (88.75)	2.80±0.52[b] (70.00)
Spiciness	3.50±0.89[b] (81.40)	3.75±0.91[b] (87.21)	4.30±0.80[a] (100)	3.80±0.81[a] (88.37)	2.85±0.75[b] (66.28)
Aftertaste	2.95±1.00[b] (71.08)	3.10±0.85[b] (74.70)	4.15±0.93[a] (100)	2.75±0.72[b] (66.27)	3.05±0.89[b] (73.49)
Warm sensation	3.05±0.89[b] (71.76)	3.30±1.03[b] (77.65)	3.20±0.89[a] (75.29)	3.15±0.88[b] (74.12)	4.25±0.91[a] (100)

N = 55, 103: Formula containing 5 g CCRs, 306: Formula containing 7.5 g CCRs, 138: Formula containing 10 g CCRs, 602: Formula containing 12.5 g CCRs, 901: Formula containing 15 g CCRs. The numbers followed by different letters in the same column indicate a significant difference on the level of α = 0.05. The hedonic scale: 1 = Dislike extremely, 2 = Dislike moderately, 3 = Neutral, 4 = Like moderately, 5 = Like extremely, CCRs: Cardamom chip rhizomes

Table 3: Physicochemical characterization of Fd-Carrhi

Compounds	Fd-Carrhi
Water (%)	98.5700±0.01
Ash (%)	0.0113±0.00
Protein (%)	0.1470±0.01
Lipid (%)	0.0050±0.00
Carbohydrate (%)	1.2670±0.00
pH (at 20°C)	5.9500±0.00
Total phenol (mg/100 g)	49.8800±0.01
Vitamin C (mg/100 g)	31.0000±0.01
Flavonoid (mg/100 mL)	83.0000±0.01

n = 3

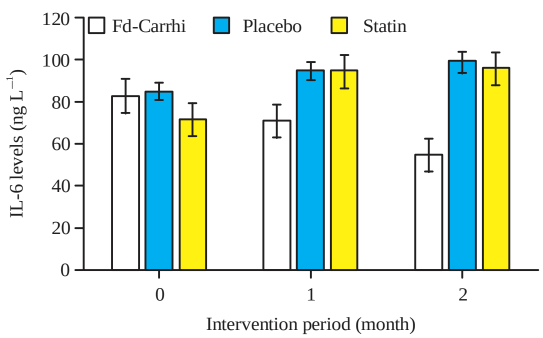

Fig. 1: Effect of Fd-Carrhi on IL-6 levels in blood plasma of atherosclerotic women
Fd-Carrhi: Group consuming statin+functional drink based on cardamom rhizome, Placebo: Group consuming statin+placebo, Statin: Group consuming statin only, n = 30, p<0.05

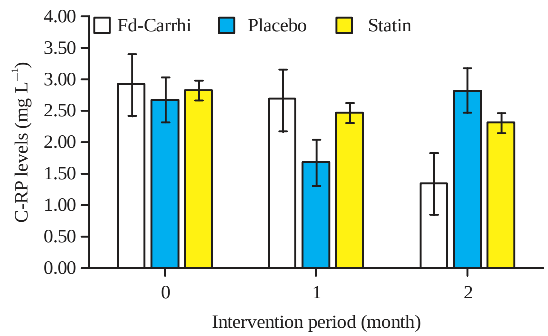

Fig. 2: Effect of Fd-Carrhi on C-RP levels in blood plasma of atherosclerotic women
Fd-Carrhi: Group consuming statin+functional drink based on cardamom rhizome, Placebo: Group consuming statin+placebo, Statin: Group consuming statin only, n = 30, p<0.05

The results of sensory tests included colour, flavour, aroma, spiciness, aftertaste and a warm sensation expressed as average values±SD. Acceptability factors (AF) for all five formulas are presented in Table 2. Test results of the physical chemistry and proximate analysis of the formula selected are described in Table 3.

The level of IL-6 was determined using the Human IL-6 Elisa Kit, SunRed-Bio. On the baseline, the three groups were homogeneous ($p = 0.84$), but after a 2 month intervention, the IL-6 level decreased from 82.67-54.69 ng L^{-1} ($p = 0.02$) in Fd-Carrhi group. The opposite result occurred in the placebo and statin group ($p = 0.53$ and $p = 0.13$) (Fig. 1).

C-RP level was determined using the Human C-RP Elisa Kit, SunRed-Bio. Three groups were homogeneous on the baseline ($p = 0.88$); however, the level decreased after the 2 month intervention from 2.92-1.34 mg L^{-1} ($p = 0.047$) in the Fd-Carrhi group, while the opposite results were obtained in the placebo and statin groups ($p = 0.67$ and $p = 0.93$) (Fig. 2).

Total cholesterol was determined using the CHOD-PAP (Cholesterol Oxidase-Peroxidase Aminoantipyrine Phenol) method. The initial total cholesterol was not different in the groups ($p = 0.60$), but after 2 month intervention, the level decreased in the Fd-Carrhi group from 291-186.3 mg dL^{-1} ($p = 3.71E-07$) and in the placebo group from 294.3-209.7 mg dL^{-1} ($p = 7.84E-05$). Despite a significant decrease in total cholesterol in the placebo group, the level was still more than normal. Cholesterol levels in the statin group remained constant ($p = 0.72$) (Fig. 3).

The initial triglyceride level (TG) was homogeneous in the groups ($p = 0.29$). After the 2 month intervention, the level decreased but not significantly in all groups and was still within the normal range (30-200 mg dL^{-1}) (Fig. 3).

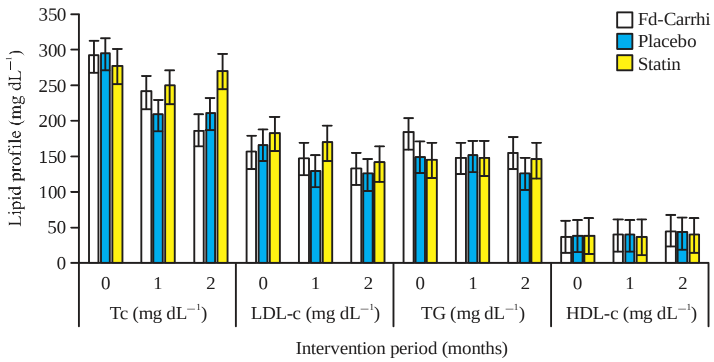

Fig. 3: Effect of Fd-Carrhi on lipid profile in blood plasma of atherosclerotic women

Fd-Carrhi: Group consuming statin+functional drink based on cardamom rhizome, Placebo: Group consuming statin+placebo, Statin: Group consuming statin only, Tc: Total cholesterol, LDL-c: Low density lipoprotein cholesterol, TG: Triglyceride, HDL-c: High density lipoprotein cholesterol, n = 30, $p<0.05$

The LDL-c level on the baseline was not different in the groups ($p = 0.23$). After the 2 month intervention, the level decreased significantly in the Fd-Carrhi, placebo and statin groups, that is, $p = 0.0009$; $p = 0.029705$ and $p = 0.006279$, respectively (Fig. 3).

Upon Fd-Carrhi consumption, the HDL-c level increased from 36.69-44.26 mg dL^{-1} ($p = 0.014$). Similarly, the placebo and statin groups experienced HDL-c increase but not significantly ($p = 0.09$) and ($p = 0.71$), respectively (Fig. 3).

Fd-Carrhi formula selected: Colour is a characteristic that determines the acceptance or rejection of a product by consumers. The first impression obtained from a food and beverage product is colour. Winarno[21] stated that the assessment of the quality of foodstuffs in general depends on several factors such as colour, taste, texture and nutritional value. However, before these factors are considered visually, colour is often more decisive than any other factor. The results of the assessment of the sensory test for colour to attribute to Fd-Carrhi can be seen in Table 2. The highest value of response-based evaluation on the acceptable colour of cardamom rhizome-based drinks was 100, expressed as 'like moderately' to formula 138, which was formulated with cardamom rhizome (10 g), with a value of 4.10 ± 0.85 (between like moderately and like extremely). The colour of formula 138 is different from the other 4 formulas ($p<0.05$). Thus, the selected colour was formula 138 with 10 g CCRs.

The flavour of the drink is a mixture of taste and aroma responses. The taste is influenced by several factors such as chemical compounds, concentration, temperature and interactions with other flavour components[21]. Flavour drinks produced from cardamom rhizomes and spices was added to the mix. A value based on the panelists for the taste of the cardamom rhizome-based drinks was 4.35 ± 0.59 (ranging between like moderately and like extremely), but formula 138 is different from the others ($p<0.05$). The addition of spices made the drink taste as the panelists preferred. Often, the flavour is not used as a parameter for functional food products, since these products have health claims that often make the products less tasty for consumption, for example, rhizome-based drinks.

Aroma is the odour generated by chemical stimulation wafted to the olfactory nerve located in the nasal cavity when the food enters the mouth. The results of the hedonic test of the aroma of Fd-Carrhi can be seen in Table 2. The highest value of a response-based evaluation on an acceptable aroma was found in formula 138 (a formula with 10 g cardamom rhizome) with a scale of 4.0 ± 0.65 (like moderately). Formula 138 is not different from formulas 306 and 602 ($p>0.05$), but formula 138 has the highest acceptable factors (100). Generally accepted by the nose and the brain as more of an herb-like aroma or a mixture of the four main aromas: fragrant, sour, rancid and charred. The aroma of food/drinks significantly determines the delicacy/freshness of the food. The possibility of a volatile essential oil and water-soluble substances in the rhizome cardamom and spices added to the formula made up the aroma preferable by the panelists, as proposed by Winarno[21].

The addition of other spices such as cinnamon, ginger and cloves also improves the taste and aroma of the product. In addition, the spice also increases the shelf life of products by acting as an antimicrobial and antioxidant. Lime leaves are known to contain essential oils that can improve the aroma of the beverage product. Efficacy of essential oils for health is quite diverse among the others, for example, as a medium for relaxation, stress management, particularly conventional antibiotics against microbes such as bacteria, viruses and fungi. In addition to the essential oil content, lime leaves contain flavonoid antioxidant compounds whose levels depend on the age of the leaf. In young leaves, the flavonoid is still low and then rises to the higher level in the growing leaf[22]. This study used old lime leaves, so the levels of flavonoids detected as total phenol are also high.

In this case, the hedonic quality test was conducted to evaluate the spiciness level of Fd-Carrhi. This product is a drink containing aromatic compounds, with a typical spicy taste[23]. Compounds contained in cardamom seeds, which may also be found in the rhizome, include saponins, flavonoids, polyphenols and essential oils. The average ratings of the panelist acceptance rate of the level of spiciness of Fd-Carrhi were 4.30$\pm$0.8, between like moderately and like extremely, in formula 138. The level of spiciness was like formula 602 ($p>0.05$) but different from formulas 103, 306 and 901 ($p<0.05$). Cardamom seeds and rhizomes may contain essential oils (mainly cineole, terpineol and borneol), which belong to the terpenes class[24]. All chemical constituents of essential oil are mixtures of compounds, never in the singular. Similarly, cardamom oil contains five major components, namely, cineole, borneol, limonene, alpha-terpinene and alpha-terpinyl acetate terpinene. When decomposed, cineole smelled delicious and spicy or astringency like eucalyptus oil. Borneol camphor smelled like mothballs; limonene was fragrant like tangerines; alpha-terpinyl acetate smelled of lime; and alpha-terpinene smelled like citrus. These compounds constitute the mixture of the five components that make the distinctive aroma of cardamom.

Aftertaste is a residual flavour or taste that remains in the mouth after eating or drinking. Fd-Carrhi has an aftertaste, preferred by the panellists. The value given by the panellists to this aftertaste was 4.15$\pm$0.93, between like moderately and like extremely and the value of the AF was 100 for the formula 138. The aftertaste of formula 138 was different from the aftertaste of formulas 103, 306, 602 and 901 ($p<0.05$). Generally, cardamom rhizomes have aromas and flavours that are less preferred, but the addition of spices to the drink allows the aroma and flavour to be closed or to interact to form the preferred aftertaste. Essential oil is a component giving a distinctive aroma, while the non-volatile oil is a component of a spicy and bitter flavouring.

Fd-Carrhi gives a warm sensation in the body, in that whoever drinks it will have his body warm. The highest value of warm sensation is 4.25$\pm$0.91, between like moderately and like extremely in formula 901 (a formula with 15 g cardamom rhizome) and 100 AF value. Statistically, the value 3.2$\pm$0.89 of formula A 901 was not different from that of 138 ($p>0.05$). Therefore, Fd-Carrhi can have the formula 901 or 138.

Determination of the selected formula was based on the highest average values of all attributes. Colour attributes were selected from formula 138 because it had the highest score and the AF was 100. Based on the taste, the selected formula is 138 with a score of like moderately and like extremely and the value of AF 100. The aroma of the product is a much-preferred formula 138, with scores above like moderately and with an AF value of 100. Panellists liked the spiciness of the formula 138 with the highest value and the AF scores are 100. The product seems to be a drink with an aftertaste favoured by many people who represented the panellists, especially on the formula 138, with scores above like moderately and AF 100. Fd-Carrhi also provides a warm sensation in the body, meaning that for every person who drank it was warm in his body. The highest warm sensation value was in formula 901, not different from formula 138. Overall, the preferred formula is 138, which contains 10 g cardamom rhizomes.

Based on the average sensory value, the acceptance rank of the drinking product ranging from high to low is formula 138, 306, 602, 103 and 901, while the rank of the quality from high to low is on the attributes of flavour, spiciness, warm sensation, aftertaste, colour and aroma.

Physical and chemical characteristic of Fd-Carrhi: The water content of Fd-Carrhi was 98.57$\pm$0.01%. This result indicates that water is the largest component of the product. It is appropriate because this functional beverage was a ready-to-drink liquid with a certain viscosity and sweet taste that panellists preferred.

The ash content of 0.0113% is lower than the ash content of fresh ginger drink (7.37%)[25]. Ash content is a parameter of the mineral content (inorganic materials) in a product. According to Al-Bataina *et al.*[26], minerals in cardamom seeds are Mg, Al, Si, P, S, Cl, K, Ca, Ti, Mn, Fe, Cu and Zn. The level of calcium and sodium in cardamom seeds is reported as 142.62 mg and 25.41 mg/100 g, respectively[27]. Rhizomes may also contain these minerals, but the levels are not as high as in the seeds. Therefore, the level is low in the liquid beverages. The protein content of Fd-Carrhi was 0.147$\pm$0.01%. According to Amma *et al.*[28], protein content in cardamom powder ranged from 11.4-13.53%, while Marongiu *et al.*[29] and Al-Bataina *et al.*[26] stated that abortion is only 1% per 0.6 g cardamom. Protein cardamom seeds are low, because in the rhizomes that have been made into liquid beverages, the level is too low. The fat content is very low (0.005$\pm$0.00%) which is actually beneficial for consumers because it will not increase body fat. Carbohydrate content was 1.267$\pm$0.00%, which is generally made of shaped fibre, starch and sugar reduction. In this study, low calorie sweetener was used as it did not increase the carbohydrate level.

It is important to know the pH value of food because pH affects the number and types of microorganisms that can grow in the food ingredients[30]. pH is also an important parameter of the acid/base level of the product. Changes in pH can cause changes in the smell, taste and colour of a product. Acids and bases are basically indistinguishable from the taste and then of the effects on the indicator. Neutralization of acids and bases always produces water.

In this study, the pH value of the Fd-Carrhi products was 5.95. A solution with pH under 7 is acidic because of the concentration of H^+ is greater than the concentration of OH^-. Therefore, Fd-Carrhi is acidic. With a low pH value, microorganisms cannot grow in the drink[31], so it is safe for consumption. This product pH is lower than the pH of red ginger juice (6.16-6.27) according to Ibrahim *et al*.[32] Chances are the higher the temperature and the longer the time of extraction brewing, the lower the pH value. pH decreases as the temperature increases because of the increase in the heat energy in the solvent (water), so more chemical components of the rhizomes dissolve in the acidic medium. The higher the boiling temperature, the faster the extraction process and more and more can be extracted. However, the low pH is also associated with higher levels of vitamin C. In this study, the vitamin C content of this beverage product of 31 mg/100 g, which turned out to be higher than the levels of acid turmeric drinks reported Mulyani *et al*.[33], implies only 0.688 mg/100 g. Fd-Carrhi feels warm in the body; for it to feel fresh when consumed, the product needs to be stored in a refrigerator.

In addition to being rich in phenolic antioxidants, cardamom rhizome-based drinks are also rich in vitamin C at 31 mg/100 g. This amount can meet 41.33% of the RDA for vitamin C a day for women aged 50-64 years. Physiological and biochemical properties of vitamin C are known as electron donating. Ascorbic acid donates two electrons of the carbon double bonds between the second and third of six carbon molecules. Vitamin C is called an antioxidant for donating electrons[34]. Vitamins can prevent the oxidation of other substances, but vitamin C undergoes oxidation. Based on the content of vitamin C, Fd-Carrhi may be called a drink rich in antioxidants that are good for health.

The content of total phenols of Fd-Carrhi was the 498.8±0.01 ppm tannic acid present in the formula for 10 g CCRs, higher than the 447.93 ppm of ginger tea[32], but lower than the value for the ginger rhizome drink (2,270-2,736 ppm) and turmeric-based drink (3,509-3,705 ppm)[35]. Generally, the antioxidant compounds also possess antiproliferation[36-37]. Allegedly, the anti-proliferation potential for Fd-Carrhi products needs to be proven in future research.

Antioxidant activity is directly proportional to total phenols; thus, the higher the phenol content, the higher the antioxidant activity[38]. This observation is also supported by Hadriyono[39] in mangosteen skin (*Garcinia mangostana* L.) where a directly proportional relationship exists between total phenolic content and antioxidant activity. In general, a compound having bioactivity as a phenol antioxidant is a compound that has a hydroxyl group substituted on the benzene ring at positions ortho and para to the -OH and -OR. Phenol compounds inhibit free radicals by donating protons to form a stable radical. The formation of a stable radical is because of free electrons contained in the radical stabilized by electron delocalization in the presence of the resonance of the aromatic ring.

Phenolic compounds are active as antioxidant because they can bind oxygen to prevent it from participating in oxidation processes. In addition, the phenolic compounds can also bind metals capable of catalysing the oxidation reaction[40]. Thus, there is a relationship between total phenolic compounds or phenol with antioxidant activity. According to Hincapie *et al*.[41], antioxidant activity with the activity of radical scavengers in the solvent extract cannot be predicted based on the total phenol content, but rather by the presence of various compounds and their interactions.

Determination of total phenols is the basis of testing the antioxidant activity, as many researchers reported that phenolic compounds prevent oxidation reactions[42-43]. The higher the phenolic compounds in Fd-Carrhi, the higher the antioxidant activity.

Antioxidant activity can be evaluated *in vitro* and *in vivo*. *In vitro* is performed by determining the levels of vitamin C and total phenol product, as this study has done[44]. An *in vivo* test is conducted by administering the beverage products to animals or humans for some time and then testing the antioxidant activity enzyme from a sample of blood or urine, for enzymes SOD, Catalase, or GSH-PX[10, 45].

Polyphenol compounds such as phenolic acids, flavonoids and tannins are widely found in plants. When based on a flavonoid cardamom rhizome, 100 mL Fd-Carrhi is equivalent to 83 mg of flavonoids in cardamom rhizomes[44]. To date, a flavonoid raw dose has not been determined. Health Supplements Nutritional Guide 2009 stated that most supplement doses are 30-200 mg/day, higher for a clinical dose (between 500-2000 mg/day) and 50-500 mg/day for therapeutic purposes. The compounds have biological activity that differs depending on the origin and the parts of the plant, so the effects on health also vary. However, most plants or parts of plants have potential to be antioxidants, as shown by their polyphenolic compounds[46-47].

Effect of Fd-Carrhi on inflammatory status: The decrease of IL-6 level in the Fd-Carrhi group may be due to the phenolic antioxidant in the drink. Hopkins *et al.*[48] stated that supplementing antioxidant can lower the IL-6 level in blood. Phenolics are heterogeneous compounds derived from plant secondary metabolism. According to Bravo[49], phenolic compounds can be classified into flavonoid and non-flavonoid. Epidemiological data showed that high phenol diets reduced the occurrence of chronic diseases such as diabetes, cardiovascular disease, Alzheimer, Parkinson and inflammation[50]. Phenolic compounds are assumed to be responsible for beneficial effects in the diseases. Chronic acute inflammation contributes to the development of chronic diseases such as atherosclerosis. Several research studies elaborated that interventions that can modify inflammation in chronic diseases are assumed to show a potential for prevention[51-52].

Several phenolic compounds show anti-inflammatory properties. Although the anti-inflammation mechanism is not thoroughly known, correlation exists between the high intake of a phenol-enriched diet and inflammation downregulation response[53]. Nieman *et al.*[54] reported that anti-inflammatory phenolic compounds lowered the TNF-α level through inhibiting nuclear factor kappa-B (NF-κB). NF-κB controls gene expression related to cytokine and chemokine pro-inflammation TNF-α, IL-1β and IL-6. As NF-κB is inhibited, IL-6 expression and the content decrease. Phenolic compounds work the same way as Non-Steroid Anti-Inflammatory Drugs (NSAIDs) such as inhibiting pro inflammation mediators besides COX by limiting the activity or expression of the genes. Moreover, some phenolic compounds increase or decrease a transcription factor such as NF-κB on the tract of inflammation and antioxidant[55-56].

The structure of phenolic compounds significantly affects the anti-inflammation mechanism. Lattig *et al.*[57] reported that unsaturated C-rings stabilized intermediate radicals through resonance. In addition, the double bond between C2 and C3 induced coplanarity between rings A and C and stimulated flavonoid interaction with the active enzyme. Eventually, the lignan of the phenolic compounds participates in formation of a covalent bond between the flavonoid and the macromolecule[58]. Meanwhile, Chuang and McIntosh[59] stated that phenolic compounds showed anti-inflammatory activity by inhibiting the synthesis of the pro-inflammation mediator, modifying eicosanoid synthesis, inhibiting activated immune cells and NOS (nitric oxide synthase) and cyclooxygenase-2 by the inhibitory effect of NF-κβ.

Some flavonoid diets are shown to modulate inflammation mediators similar to IL-6, such as flavonol (a type of flavonoid) that affects the concentration of blood plasma IL-6[60]. Epidemiological data also proved the decrease in chronic disease incidence of people taking a phenolic-enriched diet[61-62]. Every type of phenolic in extracts has a different effect on pro-inflammation mediators. For example, one type can inhibit pro-inflammation mediators while the other inhibits the expression. Therefore, Ambriz-Pérez *et al.*[63] stated that phenolic compounds, either monophenolic or combined, can serve as the alternative therapy for inflammation because of the ability to perform under diverse mechanisms, while medicine has specific work on the body. Fd-Carrhi is viable as an alternative natural diet of inflammation therapy for atherosclerotic patients.

C-RP is acute-phase protein whose level increases from chronic inflammation[64]. Epidemiological studies stated that CRP is both marker and agent of atherosclerosis development[65]. CRP is also the clinical marker for the heightened risk of cardiovascular disease[66]. *In vitro* and *in vivo* research showed that CRP served as a pro-atherogenic factor and promoted atherothrombosis[67], promoted activation and dysfunction of endothelial cells[68], affected migration and proliferation of vascular smooth muscle[69], induced changes in biological matrix[70] and promoted coagulation[71].

In an early study, CRP level of atherosclerotic patients was 2.72 ± 2.23 mg L^{-1}. However, the level significantly decreased in the Fd-Carrhi group compared to the placebo and statin groups, assumedly due to the phenolic compounds from Fd-Carrhi. Similar findings by Fito *et al.*[72] showed that IL-6 and C-RP decreased after 28 coronary heart disease (CHD) patients consumed 161 mg kg^{-1} b.wt. of phenol-rich olive oil. Phenolic protective effect of heart disease is derived from the ability to reduce thrombocyte aggregation[73], to improve vasorelaxant[74], to reduce lipid peroxidation[75] and to suppress pro-coagulant[76]. Ambriz-Pérez *et al.*[63] has traced the potential for grape phenolic that provides protection against atherosclerosis by suppressing CRP expression. The protein compounds significantly perform in atherosclerotic pathogenesis[67]. Decreasing the CRP level also occurred in the plasma of lactating mothers after consuming soy bean milk rich in isoflavone[77].

CRP serves for atherosclerosis pathogenesis because the decreased level of CRP is effective to inhibit atherosclerosis. Numerous studies have proven that CRP predicts the risk of CVD such as myocardial infarction, coronary artery disease (CAD), stroke, peripheral artery disease, even sudden death[78]. CRP is the additional marker for the 10 years risk score of predicting future CVD in healthy American women. Based on the findings above, Fd-Carrhi brings the atherosclerotic patients to the middle risk of CVD.

Effect of Fd-Carrhi on the lipid profile: High total cholesterol (Tc) and LDL-c level is the risk factor for atherosclerosis and the primary cause of CVD, but a high level of high density lipoprotein cholesterol (HDL-c) is considered the protector and anti-inflammatory[79]. Subjects in the present research suffered from hypercholesterolaemia (287.4 mg dL^{-1}), with high LDL-c (167.76 mg dL^{-1}) and low HDL-c (37.37 mg dL^{-1}). This condition is prone to CVD. However, in the Fd-Carrhi group, the Tc and LDL-c decreased but the HDL-c level increased, assumedly due to the phenolic compounds in Fd-Carrhi that decreased Tc. This result supported Winarsi *et al.*[11] that the flavonoid (one type of phenolic) of the cardamom rhizome decreased the Tc level of atherosclerotic mice induced with epinephrine. Phenolic compounds belong to the flavonoids that can inhibit the activity of HMG-CoA reductase enzyme[80], thereby, decreasing cholesterol synthesis and thus cholesterol content. Flavonoids inhibit cholesterol absorption by limiting the formation of micelles. The inhibited cholesterol absorption in the intestines is due to an insoluble flavonoid-cholesterol complex that is then bound with bile acid and excreted in the faeces. Cholestyramine, sequestrant of bile acid, distracts the circulation of enterohepatic bile acid by releasing it and preventing the reabsorption in the intestine. Consequently, the bile acid pool is reduced. The more cholesterol is converted into bile acid (to maintain a steady level in blood circulation), the lower the plasma cholesterol level. Cicerale *et al.*[81] stated that in the bodies of 200 healthy men consuming high phenolic diets, Tc/HDL-c decreased. The increasing HDL-c is not linear with the increasing phenolic[82]. Olive oil phenolic intake has improved HDL-c circulation of 5.1-6.7% in human[83]. Gimeno *et al.*[84] also reported LDL-c decreases after 1 week consumption of phenol-enriched olive oil.

The increasing HDL-c level also occurred in Fd-Carrhi subjects during 2 months, which may due to phenolic content. Mechanism of HDL-c level increased by phenolic FD-Carrhi was unclear, but Lamon-Fava *et al.*[85] confirm that flavonoid increases the production of apolipoprotein A1 (Apo-A1) and regulation of its expression through signalling pathways of mitogen-activated protein kinase. Apolipoprotein-A1 is a compound that contributes to the formation of prebeta-HDLc, which will then be converted to alpha-HDLc and then mature through the process of esterification of free cholesterol to cholesterol ester by lecithin-cholesterol acyl transferase enzyme. HDL-c is an anti-atherogenic, antioxidant, anti-inflammatory[86]. Increased concentrations of HDL-c can reduce the progression of atherosclerotic lesions.

In this study, there was no change in TG levels in the groups taking Fd-Carrhi, placebo, or statins, but the levels were within the normal range (167.76 mg dL^{-1}). According to Sudhop *et al.*[87], such levels belong to the high normal limit criteria (borderline); therefore, it needs to be controlled with Fd-Carrhi. Clearly, Fd-Carrhi is able to control the lipid profile in the body of atherosclerotic women.

CONCLUSION

Fd-Carrhi is composed of 18% cardamom rhizomes, 9% wood secang, 3.6% cinnamon, 0.3% cloves, 3.6% flower mace, 45% ginger, 13.7% lemongrass, 2.6% low calorie sugar, 0.5% salt and 3.7% orange leaves. Colour, taste, aroma, spiciness and aftertaste of the product had scores between like and extremely like, while the warm sensation scored neutral to like. Total phenol was 498.8 ppm and vitamin C was 36 mg/100 g. Fd-Carrhi can reduce the content of IL-6, C-RP, Tc and LDL-c, while increasing HDL-c content and maintaining TG level. Therefore, Fd-Carrhi can inhibit atherosclerosis towards CHD.

SIGNIFICANCE STATEMENT

This study discovers the composition of Fd-Carrhi that can be beneficial to improving the lipid profile of women with atherosclerosis. This study will help the researcher to uncover the critical areas of the Fd-Carrhi formula that many researchers were not able to explore. Thus, a new theory about composition of the functional drink rich in cardamom rhizome may be developed. In addition to the cardamom rhizome, added spices improve the organoleptic properties of this drink. Possibly, Fd-Carrhi can prevent the development of atherosclerosis at the CHD, by improving the lipid profile of the subject.

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