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EFFECTS OF NAGI CAMPHOR AND GINGER METHANOLIC EXTRACTS ON THE ATRIA CONTRACTION: IN VITRO STUDY ON ISOLATED GUINEA PIG ATRIA

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Abstract

Many medicinal herbs are used to treat some disease in Indonesia. Ginger is one of the most widely used herbs that contains several bioactive constituents and possesses health promoting properties. Nagi Camphor comes from the family of Compositae. The plant is strongly aromatic. Both Nagi Camphor and ginger are used in traditional medicine to treat various diseases like hypertension and diarrhea. The objective of this study to investigate whether Ginger and Nagi Camphor methanolic extracts have the ability to decrease atrium contractility which, in turn, decrease cardiac contraction improving this effect may lead to use both herbs to treat hypertension. The isolated atrium of guinea pig was put in the organ bath containing Kerb's solution aerated with Carbogen. Six doses of Methanolic extract of the Ginger and five doses of methanolic extract of Nagi Camphor were examined. Nor-epinephrine (10^{-4} M) was injected to the organ bath as a pre-contraction for atrium contractility. Atrium relaxation was recorded using Powerlab kit which was connected to isometric transducer (in vitro study). The result indicated that all concentrations of Nagi Camphor and Ginger reduced the atrium contraction significantly ($p<0.05$). The herbs also reduced the contractlity of the heart and these herbs maybe used to reduced hypertension.

Keywords: Ginger extract, Guinea-Pig atrium, Nagi Camphor extract, Nor-epinephrine.

INTRODUCTION

Globally, high blood pressure (BP) is estimated to cause 10.4 million deaths, about 13% of the total around the world (1, 2). Medicinal plants contain ingredients that can be used for treatment. Medicinal plants have become the leading contributor to health to mankind since time immemorial. Herbs are staging a comeback and herbal 'renaissance' is happening all over the globe(3).

Most often medicinal plants (herbal medicine) are containing some substances that work as antitoxic to the toxic effect of the main substances of those plants. These antitoxic substances can increase or decrease the effect of active compounds of the herbs.

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Those substances make the plants safer than chemical medicine. For example, Nagi Camphor which acts as diuretic and has the ability to resolve kidney problems is claimed to produce less side-effect than chemical drugs (3). Furthermore, those plants are cheaper than chemical medicine. The reasons lead us to study medicinal plants to improve treatments to many kind of diseases.

According to cardiac physiology; there are two types of cells within the heart the myocardiocytes and the cardiac pacemaker cells. Myocardiocytes make up the atria and ventricle of the heart. These cells must be able to shorten and lengthen their fibers and the fibers must be flexible enough to stretch. These functions are critical to the proper form during the beating of the heart. Cardiac pacemaker cells carry the impulses that are responsible for the beating of the heart.

They are distributed throughout the heart and are responsible for several functions. First, they are responsible for being able to spontaneously generate and send out electrical impulses. They also must be able to receive and respond to electrical impulses from the brain. Lastly, they must be able to transfer electrical impulses from cell to cell(4).

Cardiac muscle cells are electrically excitable. However, unlike the cells of other muscles and nerves, the cells of cardiac muscle show a spontaneous, intrinsic rhythm generated by specialized “pacemaker” cells located in the sinoatria and atrioventricular (AV) nodes. The cardiac cells also have an unusually long action potential, which can be divided into five phases (0–4). Illustrates the major ions contributing to depolarization and polarization of cardiac cells. These ions pass through channels in the sarcolemmal membrane(5).

Depolarization of cardiac cell is followed by re-polarization, although the inward flux of Ca++ extends the absolute refractory period and inhibits rapid sequential depolarizations. Impulses pass from the autorhythmic cardiac cells in the sinoatria node through atria myocytes to the atrioventricular node, down the atrioventricular bundle (bundle of His) to the right and left bundle branches and on to the Purkinje fibers. Cells at SA node depolarize approximately 100 times per minute.

Cells at the AV node depolarized approximately 60 times per minute and can support cardiac function if the cells of the SA node fail to function properly but are overridden by action potentials that originate in the SA node under normal circumstances. This is why the SA node is known as "the pacemaker of the heart". Fibers of the bundle branches and the Purkinje cells spontaneously depolarize about 32 times per minute but that is insufficient to supply the body.

Parasympathetic stimulation "puts the brakes on" the rate set by the SA node, resulting in a resting heart rate considerably less than 100 bpm (72-75) bpm, depending on aerobic conditioning). Sympathetic fibers innervate both the SA and AV nodes and the myocardium. Sympathetic stimulation will cause an increase in heart rate and contraction of the ventricles, especially the left ventricle (6).

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One of these herbal is Nagi Camphor. Mainly found in tropical and subtropical Asia, Africa, and Oceania such as South China and the Philippines (3), the plant is a strongly aromatic herb that grows tall and erect. Its height ranges from 1.5 to 3 meters, with stems that grow for up to 2.5 centimeters.

Coming from the family of Compositae, Nagi Camphor is safely used in cuisine. It is also an amazing medicinal plant; it is commonly used to treat hypertension because it has diuretic effect without toxicity or with less toxicity. In addition, it is useful for kidney problems [4] and also has antidiarrheal activities (7).

Ginger, another medicinal plant, is one of the most widely used herbs. It contains several bioactive constituents and possesses health promoting properties. Ginger is used as tea in many parts of the world. This herb inhibits stimulatory action on heart muscle which results in the decrease of heart beat. Moreover, in the cardiovascular system both [6]-gingerol and[(8).

Shogaol, constituents in Ginger, demonstrate hypotensive response at lower doses. At high doses, however, Ginger and Nagi Camphor might result in three phase pattern. The benefit of Ginger and Nagi Camphor i.e., their effect on the atrium contractility serves as the basis of the research. Thus, the research aimed at investigating the effects of the two herbs which have commonly been used to treat hypertension in herbal medicine.

MATERIALS AND METHODS

Sample preparation

Plant materials (Ginger and Nagi Camphor) obtained from MATERIA MEDICA, Batu City, East Java. And authenticated at the herbarium of Faculty of Medical of Brawijaya University, Ginger and Nagi Camphor were extracted by continuously refluxing of methanol in Soxhlet extractor 8- 12 hours. The obtained extract was concentrated in a rotary vacuum evaporator. The desired concentration (w/v) were prepared from this powder.

Preparation of isolated guinea pig atrium

Guinea pig neck bones were dislocated and the carotids of artery were cut. After that, the thoracic wall was opened immediately to take the whole heart organ. The heart was put into a glass containing Kreb's solution which was continuously aerated with carbogen. Then, the atrium was separated from the ventricle and then transferred into a disk which contains Kreb’s solution aired by carbogen. Both ends of the atrium were tied up and placed upright in the organ bath (size 25 cc).

One end was fixed while the other end was connected to an isotonic transducer (with weights of 0.2 grams). Then, the isotonic transducer was connected to the recorder (9).

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Pharmacological test

Male albino fasted (24 h) guinea pigs weighing 400-500 g were killed by cervical dislocated and exsanguinated. The atrium was placed in 10 ml baths filled with Kerb's solution (NaCl, 6.90; KCl, 0.35; CaCL_2, 0.28; NaHCO_3, 2.10; MgsO_4-2H_2O, 0.29; KH_2P0_4, 0.16 glucose, 2.00 g/l). (Ghosh, 1917) [7]. The solution was kept at 37ºC and oxygenated continuously. Initial tension was 0.2g and stabilization time was 45-60 min. Isometric contractions were recorded on Isometric transducer connected to a PowerLab recorder. Concentration of nor-epinephrine (10^{-4} M) were added to the bath and the contraction was constructed. Methanolic extract of two herbs were then added to the bath 5 min before the corresponding concentration recorded (Ghosh, 1917) (9)

Drugs and Solvents

Nor-epinephrine (Sigma) and Methanol 90% (Brawijaya-Pharmacology Lab). Nor-epinephrine was dissolved in distilled water and desired concentration was prepared.

Analysis of results

Contractions were expressed as bars of the mean contraction obtained from the norepinephrine of three experiments. The mean contraction of nor-epinephrine in the absence or presence of herbs (ginger and Nagi Camphor) were plotted using the Excel computer program. One Way Anova was conducted to see the significance of each dose.

RESULTS

Preliminary study of Nagi Camphor and Ginger extracts concentrations:

A) Preliminary study of Nagi Camphor concentration:

The extract was administered in five doses of 0.125%, 0.250%, 0.500%, 0.750%, 1% after a single dose of NE. The mean values of the resulting atrium contraction and the standard deviation (in average) of all concentrations of Nagi Camphor extract (0.125%, 0.250%, 0.500%, 0.750%, 1%) were presented in the following table (Table 1) (Figure 1)

Table 1: Mean and standard deviation of guinea pig atrium contraction after administration of each Nagi Camphor extract concentration

Treatment	Contraction of atrium in average Δ	Standard deviation in average Δ
NE 10^{-4} alone	1.330	0.21
(1) Nagi Camphor 0.125%+ NE 10^{-4}	0.103	0.02
(2) Nagi Camphor 0.250%+ NE 10^{-4}	0.063	0.01
(3) Nagi Camphor 0.500%+ NE 10^{-4}	0.046	0.01
(4) Nagi Camphor 0.750%+ NE 10^{-4}	0.109	0.07
(5) Nagi Camphor 1%+ NE 10^{-4}	0.137	0.09

The atrium contractility of Guinea pig which was given Nagi Camphor extract is shown in the following figure (Figure 1).

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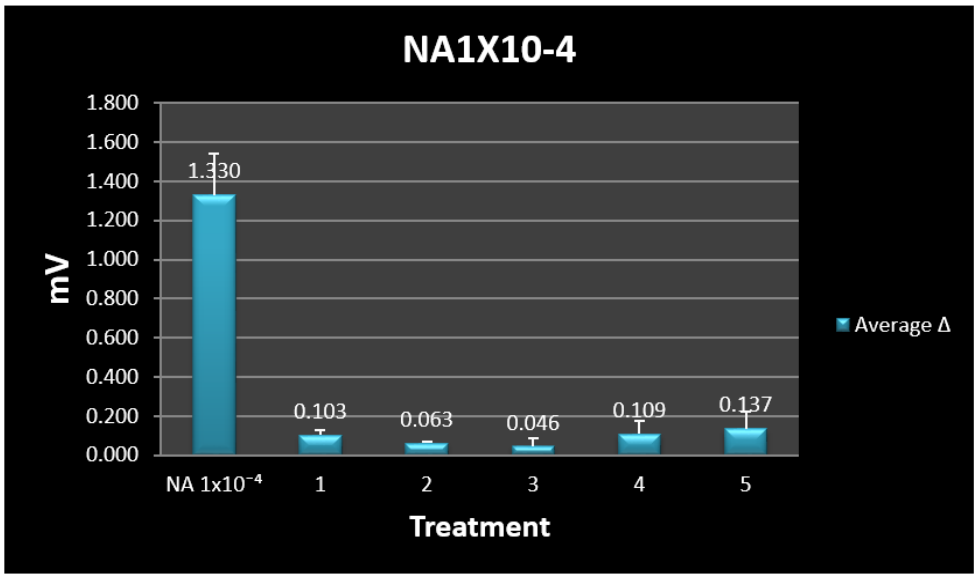

Figure 1: The contraction of Nor- Epinephrine in average after the administration of Nagi Camphor extract concentration

The result analysis showed that these groups were not significantly different from each other. This was indicated by the decrease in atrium contractility by more or less 90% after the five concentrations of Nagi Camphor extract were administered when they were compared to the control group ($p<0.05$). This signifies that the increased dose of Nagi Camphor extract did not significantly decrease atrium contractility ($p>0.05$).

B) Preliminary study of Ginger extract concentration

The doses of the Ginger extract were 0.01, 0.1, 1, 10, 100, 1000 microgram/ml. Each single dose of Ginger was proceed by NE. The mean value and the standard deviation of the three repetitions of the six Ginger concentration administrations were presented in the following table.

Table 2: Mean and standard deviation of guinea pig atrium contraction after administrations of each Ginger extract concentration

Treatment	Contraction of atrium in average Δ	Standard deviation in average Δ
NE 10^{-4} alone	0.253	**0.060**
(1) Ginger 0.01+ NE 10^{-4}	0.144	0.038
(2) Ginger 0.1+ NE 10^{-4}	0.229	0.017
(3) Ginger 1+ NE 10^{-4}	0.248	0.015
(4) Ginger 10+ NE 10^{-4}	0.289	0.060
(5) Ginger 100+ NE 10^{-4}	0.176	0.066
(6) Ginger 1000+ NE 10^{-4}	0.051	0.070

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The atrium contractility of Guinea pig given Ginger extract is shown in the following figure.

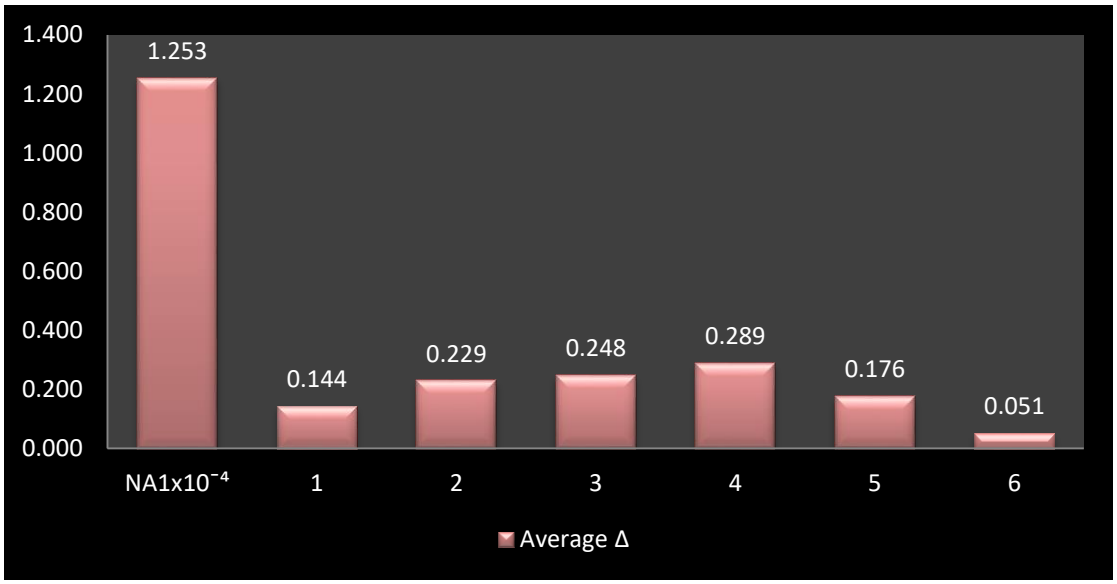

Figure 2: The contraction of Nor-Epinephrine in average after administration Ginger concentration

The result analysis showed that every group was not significantly different from each other. This is suggested by the administration of Ginger extract of concentration 0.01, 100 and 1000 which had the ability to decrease atrium contractility by more than 85 %, when compared to the control group ($p<0.05$). Doses 0.1, 1 and 10 decreased atrium contractility less effectively than the previously mentioned doses (less than 85%), when compared to the control group ($p<0.05$).

DISCUSSION

The objective of *in vitro* study were to find out whether the crude extract of Nagi Camphor and Ginger produced any effects on heart contraction and to determine the correlation between the effects of the herbs and atria contraction induced by Nor-Epinephrine. As mentioned previously, Nagi Camphor and Ginger are traditionally used to decrease heart contraction. The study, thus, was aimed this effect by investigates the mechanisms that may the two herbs work to decreasing heart contraction.

In the heart both beta1- and beta2- adrenoceptors coexist. As a rule, the amount of beta2 adrenoceptors is higher in the atria than in the ventricular myocardium. Both beta1- and beta2-adrenoceptors couple to adenylate cyclase and mediate positive inotropic effects of isoproterenol and epinephrine on isolated, electrically driven cardiac preparations. In the atria, stimulation of both beta1- and beta2- adrenoceptors causes maximal increases in contractile force; in the ventricular myocardium, however, only beta1-adrenoceptor stimulation maximally increases contractile force, whereas beta2-adrenoceptor stimulation evokes only submaximal increases. On the other hand, Norepinephrine induces its positive inotropic effect on atrial and ventricular preparations solely via beta1-

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adrenoceptor stimulation. Because norepinephrine is the main transmitter of the human sympathetic nervous system, this indicates that under normal physiological conditions, the heart rate and contractility are under the control of cardiac beta1-adrenoceptors, whereas cardiac beta2-adrenoceptors play only a minor role, if at all. However, in situations of stress, when large amounts of epinephrine (acting at both beta1- and beta2 adrenoceptors with the same affinity) are released from the adrenal medulla, activation of cardiac beta2- adrenoceptors may contribute to an additional increase in heart rate and/or contractility. In chronic heart failure, cardiac beta-adrenoceptor function decreases (presumably due to endogenous "down-regulation" by the elevated catecholamines), and this decrease is related to the severity of the disease (10). Therefore, atria was used in the research because of the β- receptors (β_1 and β_2). Beta-receptor activation results in increased calcium influx in cardiac cells. This has both electrical and mechanical consequences which lead to the increase of atria and ventricular contraction (11).

To see the effect of Nagi Camphor and Ginger extract on atria contraction, the research had to create a condition in which guinea pig atria contracts vigorously. The possibility of both Nagi Camphor and ginger work on β_1 adrenergic receptor. In the research Nor-Epinephrine was used to induce the contraction of atria. Nor-Epinephrine works by binding on β_1 receptor which activates Gs proteins, the Gs linked to adenylate cyclase. Agonist binding thus causes a rise in the intracellular concentration of the second messenger cAMP. Downstream effectors of cAMP include cAMP-dependent protein kinase (PKA), which mediates some of the intracellular events following hormone binding. The increasing of intracellular calcium is mainly responsible for heart contraction and this kind of receptors (β_1) is found in smooth muscles of atria. Consequently, nor-epinephrine increases peripheral resistance and both diastolic and systolic blood pressure. Compensatory vagal reflexes tend to overcome the direct positive chronotropic effects of Nor-Epinephrine. Nor- Epinephrine has relatively little effect on β_2 receptors (12)

The result of the data analysis on atria contraction after the administration of five concentrations of Nagi Camphor and six concentrations of Ginger extracts showed that all concentrations effectively decreased the contraction of atria. However, the relaxation effect of Nagi Camphor doses were more than Ginger doses. From 3 repetitions of the doses, the mean of atria contraction for each concentration was obtained. The administration of various doses of Nagi Camphor and Ginger extract can decrease atria contraction significantly ($p<0.05$). This result shows that there is relationship between extract concentration and the response of atria contraction. The effect of extract concentration on the decreased contraction is regulated by the active compound in Nagi Camphor and Ginger extracts.

Based on the research that had been done by Hoe SZ et al, 2011; Omar et al, 2012 and Hien-Kun et al, 2013, there is a mechanism probably can cause atrial smooth muscle relaxation by blocking calcium channel. This mechanisms that Nagi Camphor acts as calcium channel blocker. Ca2+ that enters the cells via the L-type Ca2+ channel during depolarization triggers the release of additional free calcium ions into the cytosol from an intracellular compartment, the sarcoplasmic reticulum (SR). Furthermore, positive

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inotropic effect can result from the stimulation of selective β1-adrenoceptors agonists, for example, albuterol and dobutamine. The drugs activate the G stimulatory protein linked to an adenylyl cyclase, which in turn, dephosphorylates an adenosine triphosphate (ATP) molecules. The resulting cAMP activates a protein kinase that induces the opening of calcium channels. This leads to an increase in calcium ions entering through the plasma membrane and thus an increased concentration of the cations within the SR (13, 14). The activation of the protein kinase also triggers the accumulation of Ca2+ originating from the SR itself. These free calcium ions interact with troponin C proteins. This activates the cross-bridge interactions between actin filaments and myosin cross bridges, thus leading to cardiac muscle cell contraction. The global and simultaneous contractions of several cells lead to heart tissue contraction (12). Therefore research hypothesis stating that Nagi Camphor extract decrease the contraction of isolated atrial of guinea pig was proved. In addition, the relaxation effect of Nagi Camphor probably due to the active compounds such as flavonoids and sesquiterpene lactones (14)) and pyrrolizidine alkaloids which is responsible for antihypertensive effect (14).

The study of Hien-Kun, 2013 demonstrated that the active constituents (Flavonoids) of Nagi Camphor have vasodilatory effect which may also be due to the opening of potassium channels and the stimulation of prostacyclin production. In which K+ regulate the action potential duration in cardiac muscle and potassium channels may also be involved in maintaining vascular tone and eventually vasodilator effect. Furthermore, stimulation of prostacycline (PGI2) production in which PGI2 binds to endothelial prostacyclin receptors and start raising of cAMP levels in the cytosol. This cAMP then goes on to activate protein kinase A (PKA). PKA then continues the cascade by dephosphorylating the myosin light chain and inhibiting myosin light-chain kinase, which leads to smooth muscle relaxation and vasodilation (12). Depend on this research which also support our result that Nagi Camphor have vasodilatation effect on guinea pig ileum.

Other mechanisms of Nagi Camphor extract which may give the relaxation effect by affecting on SA node. The mechanism of negative inotropic activities of the polar compound(s) may be attributed to a direct action on the SA node, which leads to the decrease in conduction or to the depression of myocardium of the heart, similar to the effect of quinidine, b-adrenergic blocker drugs, or calcium channel blockers.

The sino-arterial (SA) node acts as the primary pacemaker of the heart and its regular spontaneous activity is thought to rely predominantly on the sequential activation of various ion currents across the sarcolemma e.g. the possibility that calcium released from sarcoplasmic reticulum (SR) might play an important role in regulating pacemaker activity in the mammalian SA node. When SA node fires it causes increase of the heartbeat. A rise in intracellular calcium was observed prior to the rapid face of the calcium transit and before the upstroke of the action potential. It remains to be established whether calcium release from the SR might be triggered by Ca2+ entry through T-type calcium channel or L-Type calcium channels (15).

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Data analysis of atria contraction after the administration of 6 concentrations of Ginger extract, showed that all concentrations decreased atria contraction by around 85%, when compared to the control group ($p<0.05$). This implies that the administration of Ginger extract can decrease atria contraction significantly ($p<0.05$). However, considering the fact that doses 0.1, 1, and 10 mg/ml decreased heart contraction by less than 85%, while doses 0.01, 100, and 1000 decreased heart contraction by more than 85%, it can be concluded that there is unclear relationship between concentrations and the response of atria contraction. This result may show that the Ginger extract contain so compounds that work on Na+/K+-ATPase, this mechanism may explain the result of Ginger**.**

The active constituents of Ginger may inhibit the cellular Na+/K+-ATPase. This ion transport system moves sodium ions out of the cell and brings potassium ions into the cell. This transport function is necessary for cell survival because sodium diffusion into the cell and potassium diffusion out of the cell down their concentration gradients would reduce their concentration differences (gradients) across the cell membrane over time. Loss of these ion gradients would lead to cellular depolarization and loss of the negative membrane potential that is required for normal cell function. When the Na+/ K+–adenosine triphosphatase is markedly inhibited by some of Ginger active constituents (and for long term), the resting membrane potential may increase (–70 mV instead of –90 mV), which makes the membrane more excitable and increase in contractility (16)

The active constituents (gingerol and shogaol) have been studied for their cardiovascular effects in laboratory animals. Considered as the main active constituents of Ginger (17, 18), both were found to produce depressant responses when injected intravenously at low dose. Gingerol and shogaol, after being injected intravenously, triggers a triphasic response, consisting of an initial hypotensive followed by a sharp hypertensive and then a delayed hypotensive effect, at high doses in rats under anesthesia. The research result agreed with Ghayur at el, 2004 and that may explain the effect of Ginger doses on isolated guinea pig atrium (18)

According to the research that had been done by Singh *et al,* 2010 and Satyanand *et al*, 2013, there is a mechanism of Ginger which may probably can cause atrial smooth muscle relaxation by blocking calcium channel (19, 20).

The mechanism of the active substance which decrease the contraction of atria has been reported. Some studies believe that [6]- gingerol cause inhibition of Ca2+ bump on the sarcoplasmic reticulum. [8]-gingerol has exhibited positive inotropic and chronotropic effects on the left atria of guinea pigs. [10]-gingerol cause significant positive inotropic (2). Ginger extract blocks a calcium channel which would normally induce the contraction of the smooth muscle tissue found in organs and arterial walls. The reduction in smooth muscles contraction result in more relaxed atria wall that allows blood to flow more freely and at a lower pressure. In the isolated guinea pig paired atria, the extract depresses the force and rate of spontaneous atria contractions in a dose-dependent manner, similar to verapamil, a standard calcium antagonist. The methanolic extract of dried Ginger was devoid of any activity on the systolic BP or heart rate in conscious rats when given orally (20).

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The research hypothesis stating that Ginger extract decrease the contraction of isolated atrial of guinea pig was proved. In addition, the relaxation effect of Ginger probably due to the active compounds such as gingerol and shogaol (18). However, the previous study concluded that Ginger doses decrease contractility by blocking calcium channel.

In this research, the exact mechanism of the herbs was not clear. The suggestions for the future research are to use lower doses of Nagi Camphor and Ginger. Furthermore, some doses of Ginger decrease contractility of atrium more than others which give us a possibility working on K+-Na+ ATPase, the suggestion is to see the effect of Ginger doses on K+-Na+ ATPase.

Next, the cumulative doses of Norepinephrine should be given to find out the dose response curve proceeded by a single dose of Ginger or Nagi Camphor and to find the exact mechanism of these herbs on β1-receptor. Besides that, different lower and bigger doses of Nagi Camphor and Ginger should be used.

Besides that, the concentrations of Ginger and Nagi Camphor extracts in order to find the concentration that may give atrium relaxation until the baseline (normal). The side effect of this herb towards body system must evaluated in order to know the safety of using these herb. Furthermore, the toxicity test must be done in the future research. The effectiveness of the potential substances from Ginger and Nagi Camphor as hypertension for people who used to use the traditional herbs to treat the hypertension must be further examined by doing clinical testing (throught phase1 to phase 4) in order to observe the side effect and the therapeutic effects towards human.

As a conclusion, the research had proved that the administration of methanolic extract of Ginger or Nagi Camphor on atrial of guinea pig pre-contracted by nor-epinephrine can decrease the atrial contractility.

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