Centella Asiatica Effect in A High Fat and Fructose Diet-Induced Model of Metabolic Disorder in Rats

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J Biochem Technol (2021) 12(1): 1-5
https://doi.org/10.51847/GzeDdExlEH
ISSN: 0974-2328

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Received: 20 November 2020 / Received in revised form: 10 February 2021, Accepted: 04 March 2021, Published online: 11 March 2021

Abstract

*Centella asiatic*a (CA) has been reported to have a protective effect on cardiovascular disease and cardiovascular disease-related conditions. Frontal QRS-T angle is a non-invasive biomarker that can predict cardiovascular mortality and morbidity in all causes of death. This study aimed to establish the protective effect of CA in animal models of metabolic disorders and its effect on the risk of cardiac ischemia by measuring the wide frontal QRS-T angle in animal models induced by high-fructose and high-fat diets. The study was carried out on thirty male Wistar rats distributed in 6 groups (n=5): groups 1 and 2 received (distilled water), group 3 received captopril 2.5 mg/kg, group 4-6 received 50, 100, 200 mg/kg of CA leaf extract, respectively for 14 days. All groups except the normal group received a 40% high-fat diet and 25% fructose in drinking water for 28days. Test drugs begin to be administered on days 15-28. CA leaf extract showed an antihypertensive effect and reduced body weight and triglyceride level, as well as the risk of cardiac ischemia, which was significantly different in comparison to the control group ($p < 0.05$). It was concluded that CA has an impact on reducing the risk of mortality and morbidity due to cardiovascular events in metabolic disorder.

Keywords: *Centella asiatica*, Cardiovascular, Frontal QRS-T angle, Hypertension, Triglyceride

Introduction

Cardiovascular diseases (e.g. hypertension) have globally become the leading cause of death (Rashid *et al*., 2018; Taheri *et al*., 2019). However, this should be prevented long before the development of real events by identifying high-risk individuals through accurate risk stratification (Wang *et al*., 2017; Alzahrani *et al*., 2019). The spatial QRS-T angle as a biomarker is believed to be able to predict cardiovascular events (Vasan, 2006). The frontal QRS-T angle represents the deviation between ventricular depolarization and its repolarization and has an accurate predictive value (Zhang *et al*., 2015). Most studies have proven that a wide QRS-T angle predicts a poor prognosis (Borleffs *et al*., 2009), and it is a marker at a higher risk of cardiovascular disease (Oehler *et al*., 2014).

Patients with a wide QRS-T angle have a 40% risk of death from any cause and a 71% risk of dying from the heart compared with those with a normal QRS-T angle (Zhang *et al*., 2015). Furthermore, there has been a lot of evidence showing that hypertriglyceridemia is associated with atherosclerosis (Peng *et al*., 2017).

Epidemiological studies show that risk factors including obesity and high triglycerides often coincide with hypertension and can significantly increase the risk of target organ damage due to cardiovascular events or disease severity (Eckel *et al*., 2010). A cohort study reported that hypertriglyceridemia accompanied by hypertension was predicted to triple the risk of death, and a fivefold increase in cardiovascular mortality (Dolgalev *et al*., 2019).

Previous studies have reported that *Centella asiatica* in combination with turmeric can reduce blood pressure and arterial stiffness in animal models of fructose-induced hypertension and high-fat diets (Zakaria & Hasimun, 2019). *Centella asiatica* has the potential to be developed as a nutraceutical therapy that can reduce the risk of cardiovascular events in metabolic syndrome disorders. This study aimed to establish the protective influence of CA in animal models of metabolic disorders and its effect on the risk of cardiac ischemia by measuring the wide frontal QRS-T angle in animal models induced by high-fructose and high-fat diets.

Materials and Methods

Plant Material

The material tested in this study was *Centella asiatica* leaf obtained from Manoko Plantation, Lembang, Bandung, Indonesia. Botany verification was carried out at the Biological Laboratory, School of Biological Science and Technology, Bandung Institute of Technology (5234/I1.CO2.2/PL/2018). Fresh material was cleaned from impurities through running water. Then, the leaves were cut and thinly sliced and dried in an oven at 37°C. The dry material was obtained, mashed using a blender, and extracted by 70% ethanol solvent for 3 days in a room protected from light. The filtrate was filtered and concentrated in a rotary evaporator until a thick extract was collected.

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Animals and Design Study

30 male Wistar rats aged 2-3 months were kept in the Animal Laboratory of the Faculty of Pharmacy, Bhakti Kencana University, and received full access to normal food and ad libitum drinking water with a 12h dark-light cycle. They were randomly distributed in 6 groups (n=5): groups 1 and 2 received (distilled water), group 3 received captopril 2.5 mg/kg, group 4-6 received 50, 100, 200 mg/kg of CA leaf extract, respectively for 14 days. All groups except the normal group received a 40% high-fat diet and 25% fructose in drinking water for 28days. Test drugs were given on the 14th day for 14days. All procedures on laboratory animals have been accepted by the Faculty of Medicine Ethics Committee, Padjadjaran University Bandung, Indonesia (384/UN6.KEP/EC/2019).

Systolic and Diastolic Blood Pressure Measurement

On the 28th day, systolic and diastolic blood pressure measurements were taken using Kent Scientific Corporation's CODA TM.

Serum Triglyceride Measurement

On the 28th day, blood was taken and serum triglyceride levels were measured by spectrophotometry using a triglyceride reagent kit from Proline.

Measuring the Spatial QRS-T Angle and Heart Rate Derived from Electrocardiogram

The frontal QRS-T angle was measured on the 28th day using the method previously reported (Zakaria & Hasimun, 2019). In summary, this method was carried out by using a combination of sensor electrocardiogram (ECG) and photoplethysmogram (PPG). The differences in wide frontal QRS-T angle between the control and CAE groups indicated the effect of CAE on cardiovascular risk (cardio-protective effect). Heart rate was measured by calculating the distance of the R-R waves obtained from 2 cycles of PQRS-T waves in an electrocardiogram (EKG).

Statistical Analysis

One-way ANOVA was used for data analysis, performed with SPSS version 18 software. Data were presented as mean±SD. P-values < 0.05 were considered significant.

Results and Discussion

Effect of High-Fructose and High-Fat Diet on the Development of the Metabolic Syndrome

The results of systolic and diastolic blood pressure measurements on day 28 are presented as mean arterial pressure (MAP) in **Table 1**. The group that received 25% fructose in drinking water and a high-fat diet revealed a 20% increase in body weight (achieving the criteria for obesity increases body weight by 20% or more). In addition, there were increased in arterial blood pressure, serum triglyceride levels, and spatial QRS-T angle compared with the normal control group ($p < 0.05$), **(Table 1)**.

Table 1. Bodyweight, hemodynamic parameter (MAP, HR), triglyceride serum level, and frontal QRS-T angles for treatment groups at 28th Day (n=5)

Treatment Group	Bodyweight (g)	MAP (mmHg)	HR (beats/min)	TG (mg/dL)	QRS-T-angles (°)
1	234.8±8.7	87.6±2.0	371±2.5	95±2.7	86.50±2.9*
2	280.8±10.3	186.4±2.6	656±2.1	193±2.0	120.0±1.0
3	247.2±10.9	101.7±2.4	450±2.1	152±5.9	114.8±1.3*
4	245.6±12.5	101.4±1.5	449±1.2	138±2.1	109.1±1.6*
5	243.0±10.6	99.8±1.8	448±0.6	126±1.0	104.0±1.3*
6	239.6±10.6	99.2±2.5	447±1.0	106±4.7	102.5±1.4*

*Significantly different from group 2 ($p<0{,}05$). Groups 1 & 2 received drug carriers; group3 received captopril 2.5mg/kg; group 4-6 respectively received 50, 100, 200 mg/kg of *Centella asiatica* extract. Group 2-6 received a high-fructose and high-fat diet for 28days. HR (heart rate), MAP (mean arterial pressure), TG (triglyceride serum level). QRS-T angle (The angles measured in the frontal plane of the QRS axis and the T wave axis obtained from the standard 12-lead electrocardiogram)

Effect of CAE on Mean Arterial Pressure (MAP) and Heart Rate

It is apparent that the group receiving *Centella asiatica* extract (CAE) showed a decrease in blood pressure and heart rate. compared with the positive control group ($p < 0.05$), **(Table 1)**. The positive control group noted an increase in heart rate, in relation to the change in arterial blood pressure **(Table 1)**. This suggests a link between heightened blood pressure and heart rate. In line with a decrease in arterial pressure, the group that received the CAE demonstrated a decrease in heart rate.

Effect of CAE on Metabolic Disorders in Animal Models

The groups receiving CAE (50, 100, and 200 mg/kg doses) demonstrated a decrease in serum triglyceride levels, body weight, and also spatial QRS-T angle. These effects were in line with the increase in dose, which differed significantly compared to the positive control group ($p < 0.05$).

Animal models characterized by metabolic disorders occurred through the induction of feed containing high fat and high fructose in Wistar rats for 28 days. This induction results in a rise in systolic and diastolic blood pressure, heart rate, serum triglycerides, and its impact on the risk of cardiac ischemia through non-invasive frontal QRS-T angle parameters. This suggests that the formed animal models have been metabolically disrupted, including obesity, hypertension, hypertriglyceridemia, which changes the QRS-T angle value (**Table 1**).

Hypertension accompanied by hypertriglyceridemia animal models can be obtained by giving a high-fructose diet for several days or in combination with a high-fat diet (Kaprinay *et al*., 2017). Excessive consumption of fructose causes cardiometabolic diseases including hypertension and hypertriglyceridemia. Excessive fructose intake increases adiposity and leptin resistance resulting in an increase in calorie intake, which causes obesity. The state of leptin resistance accompanied by a high-fat diet affects lipid metabolism resulting in increased circulation of triglycerides in the form of very low-density lipoprotein (VLDL) (Hannou *et al*., 2018). Fructose absorption in the intestine also increases salt absorption which is thought to influence the rise in blood pressure (Klein & Kiat, 2015).

In obese patients, lipid metabolism disorders are very predominantly reported (Debata & Kumar, 2019). Dyslipidemia is present in around 60-70 percent of obese patients. In obese patients, lipid disorders include elevated serum triglycerides, VLDL, apolipoprotein B, and non-HDL cholesterol levels. The rise in serum triglycerides is due to increased liver production of VLDL particles and decreased clearance of lipoproteins rich in triglycerides. Obese patients are at increased risk of developing cardiovascular disease (Feingold & Grunfeld, 2018).

Anti-obesity and antihyperlipidemic activity in animal studies have been confirmed in *Centella asiatica* (CA) leaves (Hussin *et al*., 2009). The fraction of *Centella asiatica* ethanol extract can reduce triglyceride levels in animal models of oxidative stress (Zhao *et al*., 2014). The main active compound in *Centella asiatica* is triterpenoid, as well as asiatic acid, which is responsible for the effects of vascular repair on hypertension (Gohil *et al*., 2010). Triterpenoid fraction showed antihypertensive activity in animal models (Pramono & Nugroho, 2014). Clinical study results of triterpenoid fraction given for 4 weeks in patients with microangiopathic venous hypertension, showed improvement in symptoms and the rate of capillary filtration. Phytochemical studies have indicated that in addition to the content of triterpenoid compounds, *Centella asiatica* extract has a high content of active flavonoid compounds, including quercetin, myricetin, and kaempferol. Centella asiatica's strong antioxidant capacity is highly potent to be developed as a functional food that is currently in increasing interest due to its health benefits (Mustafa *et al*., 2010).

Asiatic acid has demonstrated antioxidant and anti-inflammatory activity as a triterpenoid active compound of *Centella asiatica*, as indicated by the improved metabolic and hemodynamic disorder (Pakdeechote *et al*., 2014). Moreover, it has the potential as an anti-obesity. It reduces body weight, leptin resistance, and plasma lipid levels including triglycerides in animal models induced by high-fat diets (Rameshreddy *et al*., 2018).

It has been reported that metabolic syndrome is strongly associated with the widening of the QRS-T angle (Delhey *et al*., 2020; Erdogan *et al*., 2020). Cardiovascular risk factors in hypertensive patients were not adequately assessed by their target blood pressure. An early biomarker is a deviation between the direction of ventricular depolarization and repolarization. This suggests a shift in repolarization or disruption in systemic hypertension where ECG is not detectable (Dilaveris *et al*., 2001). The frontal QRS-T angle is an independent predictor of coronary atherosclerosis (Dogan & Kahraman, 2020). Moreover, a wide frontal QRS-T angle correlated positively with increased markers of inflammatory activity such as IL-1, Il-4, Il-6, and TNF-α, in hypertensive patients (Sandstedt *et al*., 2020).

It has been reported that *Centella asiatica* has a good protective effect against oxidative stress (Zhao *et al*., 2014). It happens through inhibition of membrane lipid peroxidation thereby preventing oxidative damage to cardiac cells (Kumar *et al*., 2015). Also, *Centella asiatica* was reported to be able to inhibit cardiac vascular remodeling in an animal model of hypertension, thereby maintaining the integrity of the extracellular matrix (Sulistyowati *et al*., 2019).

Altogether, it is evident that this hypertensive animal model showed a widening in frontal QRS-T angle. This frontal QRS-T angle is shown to be strongly correlated with a metabolic disorder indicated by an increase in blood pressure, heart rate, body weight, serum triglyceride levels. Improvement in the QRS-T frontal angle has implications for lowering the risk of hypertensive cardiovascular mortality and morbidity. Further research needs to be done to determine the active compounds in *Centella asiatica* that are responsible for these effects.

Conclusion

Leaves extract of *Centella asiatica* has a protective effect on metabolic disorder by lowering mean arterial pressure (MAP), serum triglyceride levels, normalizing heart rate, preventing weight gain, as well as reducing widened frontal QRS-T angle. *Centella asiatica* has an impact on reducing the risk of mortality and morbidity due to cardiovascular events in metabolic disorder. Further study is needed regarding these results.

Acknowledgment: The author would like to thank the Ministry of Research and Technology of the Republic of Indonesia through Basic Research grant no. 0001 / P3M / E.PE / III / 2019.

Conflict of interest: None

Financial support: Basic Research Grants from The Ministry of Research and Technology of the Republic of Indonesia.

Ethics statement: All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

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