Research Article

แกลลิกแอซิดบรรเทาภาวะความดันเลือดสูง ภาวะดื้ออินซูลินและภาวะไขมันในเลือดสูงในหนูแรทที่มีภาวะเมแทบอลิกซินโดรมเนื่องจากได้รับอาหารที่มีน้ำตาลฟรุกโทสสูง

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บทคัดย่อ

แกลลิกแอซิดบรรเทาภาวะความดันเลือดสูง ภาวะดื้ออินซูลินและภาวะไขมันในเลือดสูงในหนูแรทที่มีภาวะเมแทบอลิกซินโดรมเนื่องจากได้รับอาหารที่มีน้ำตาลฟรุกโทสสูง

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ว. เภสัชศาสตร์อีสาน 2562; 15(1) : 158-165

รับบทความ : 18 มีนาคม 2561 **แก้ไขบทความ:** 11 พฤษภาคม 2561 **ตอบรับ:** 16 ตุลาคม 2561

แกลลิกแอซิดเป็นสารประกอบกลุ่มฟีนอลิคที่พบมากในผักและผลไม้ แกลลิกแอซิดมีฤทธิ์ต้านอนุมูลอิสระ ต้านน้ำตาลในเลือดสูง และต้านไขมันในเลือดสูง การศึกษานี้มีวัตถุประสงค์เพื่อประเมินผลของแกลลิกแอซิดต่อความดันเลือด ภาวะดื้ออินซูลินและภาวะไขมันในเลือดสูง ในหนูแรทที่มีภาวะเมแทบอลิกซินโดรมเนื่องจากได้รับอาหารที่มีน้ำตาลฟรุกโทสสูง **วิธีดำเนินการวิจัย:** หนูแรทเพศผู้สุ่มแบ่งออกเป็น 4 กลุ่ม: กลุ่มควบคุม กลุ่มเมแทบอลิกซินโดรมได้รับสารหลอก กลุ่มเมแทบอลิกซินโดรมได้รับแกลลิกแอซิด 20 มก/กก./วัน และกลุ่มเมแทบอลิกซินโดรมได้รับเมทฟอร์มิน 100 มก/กก./วัน หนูแรทจะได้รับอาหารที่มีน้ำตาลฟรุกโทสสูงเป็นเวลา 18 สัปดาห์ เพื่อเหนี่ยวนำให้เกิดภาวะเมแทบอลิกซินโดรม และได้รับการป้อนด้วยแกลลิกแอซิด หรือเมทฟอร์มิน หรือสารหลอกใน 4 สัปดาห์สุดท้ายของการทดลอง เมื่อสิ้นสุดการทดลองทำการวัดความดันเลือด ทดสอบความทนทานต่อน้ำตาล วัดระดับอินซูลินในซีรัม ระดับ the homeostasis model assessment of insulin resistance (HOMA-IR) score และระดับไขมันในเลือด **ผลการวิจัย:** แกลลิกแอซิดหรือเมทฟอร์มินลดความดันเลือด ลดระดับซีรัมอิซูลิน ลดค่า HOMA-IR score และปรับปรุงความทนทานต่อน้ำตาล ในหนูแรทที่มีภาวะเมแทบอลิกซินโดรมเนื่องจากได้รับอาหารที่มีน้ำตาลฟรุกโทสสูง ($p < 0.05$) นอกจากนี้แกลลิกแอซิดหรือเมทฟอร์มินยังสามารถลดค่าคลอเรสเตอรอลรวมและไตรกลีเซอไรด์ในเลือดให้กลับสู่ระดับปกติอีกด้วย ($p < 0.05$) **สรุปผลการวิจัย:** จากผลการศึกษาแสดงให้เห็นว่าแกลลิกแอซิดสามารถลดความดันเลือด ลดระดับไขมันในเลือด และเพิ่มความไวต่ออินซูลิน ในหนูแรทที่มีภาวะเมแทบอลิกซินโดรมเนื่องจากได้รับอาหารที่มีน้ำตาลฟรุกโทสสูง ดังนั้นอาจจะสามารถประยุกต์ใช้แกลลิกแอซิดในการรักษาภาวะเมแทบอลิกซินโดรม

คำสำคัญ: แกลลิกแอซิด, ภาวะความดันเลือดสูง, ภาวะดื้ออินซูลิน, ภาวะไขมันในเลือดสูง

Gallic acid ameliorates hypertension, insulin resistance and dyslipidemia in high-fructose diet-induced metabolic syndrome rats

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Abstract

Gallic acid ameliorates hypertension, insulin resistance and dyslipidemia in high-fructose diet-induced metabolic syndrome rats

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IJPS, 2019; 15(1) : 158-165

Received: 18 March 2018 **Revised:** 11 May 2018 **Accepted:** 16 October 2018

Gallic acid is a naturally abundant plant phenolic compound found in vegetables and fruits. It has been shown to have potent antioxidant, antihyperglycemic and antidyslipidemic activities. The present study aims to evaluate the effects of gallic acid on blood pressure, insulin resistance, and dyslipidemia in rats with metabolic syndrome induced by high-fructose diet (HFD). **Methods:** Male Sprague-Dawley rats were randomly assigned into 4 groups: normal control group, metabolic syndrome treated with vehicle group, metabolic syndrome treated with gallic acid 20 mg/kg/day group, and metabolic syndrome treated with metformin 100 mg/kg/day group. Rats were fed with HFD for 18 weeks to induce metabolic syndrome. Oral administration of gallic acid, metformin, or vehicle was performed in the last 4 weeks. Blood pressure, oral glucose tolerance test (OGTT), serum insulin level, the homeostasis model assessment of insulin resistance (HOMA-IR) score, and lipid profiles were evaluated. **Results:** Treatment with gallic acid or metformin significantly reduced blood pressure, serum insulin concentration and HOMA-IR score as well as improved glucose tolerance in HFD-induced metabolic syndrome rats ($p < 0.05$). In addition, gallic acid or metformin markedly normalized plasma total cholesterol and triglyceride levels ($p < 0.05$). **Conclusion:** These findings indicate that gallic acid attenuated signs of metabolic syndrome induced by HFD in rats. It could be suggested that gallic acid supplementation is a beneficial complementary agent for metabolic syndrome treatment.

Keywords: gallic acid, hypertension, insulin resistance, dyslipidemia

Introduction

Metabolic syndrome is a cluster of physiological and metabolic abnormalities characterized by central obesity, impaired glucose tolerance, hypertension, and dyslipidemia (Oron-Herman *et al.*, 2008). It is an early state of type 2 diabetes mellitus and cardiovascular disease, resulting in reduced quality of life and increased risk of mortality and morbidity (Isomaa *et al.*, 2001; Zimmet *et al.*, 2001). High-fructose diet (HFD)-induced insulin resistance and metabolic syndrome in laboratory animals has been widely accepted as a model for metabolic and cardiovascular abnormalities seen in metabolic syndrome in humans. Recent findings support the idea that excessive fructose intake is responsible for the epidemic of cardiovascular disease and metabolic syndrome in human (Johnson *et al.*, 2007). Furthermore, rats fed a HFD develop a well characterized metabolic syndrome, generally resulting in impaired glucose tolerance, dyslipidemia, and hypertension (Prabhakar *et al.*, 2015).

Gallic acid is a common polyphenol, widely found in hazel, tea leaves, oak bark, grapes, different berries as well as wine, and a powerful antioxidant (Erol-Dayi *et al.*, 2012; Kim *et al.*, 2016). Antioxidant, antihyperglycemic, antihyperlipidemic and antihypertensive effects of gallic acid have been reported in several studies (Bak *et al.*, 2013; Hsu and Yen, 2007). Jin et al. showed that gallic acid reduced blood pressure and suppressed oxidative stress in spontaneously hypertensive rats (Jin *et al.*, 2017). In a previous study of streptozotocin-induced diabetes in rats, gallic acid decreased the levels of blood glucose and lipid peroxidation products via restoring antioxidant enzymes activity (Punithavathi *et al.*, 2011a). Furthermore, gallic acid reduced serum total cholesterol, triglyceride and LDL-cholesterol concentration, and at the same time markedly increased HDL-cholesterol level in streptozotocin-induced diabetic rats (Latha and Daisy, 2011).

Although a wide range of potentially therapeutic effects of gallic acid have been reported, the effects of gallic acid on blood pressure, insulin sensitivity and hyperlipidemia in metabolic syndrome rats remain unknown. Therefore, the present study was designed to determine whether gallic acid can reduce blood pressure, improve insulin sensitivity, and ameliorate hyperlipidemia in rats with metabolic syndrome induced by HFD. Metformin, a standard antidiabetic drug for attenuating insulin resistance and metabolic syndrome in fructose-fed rats was used as a positive control in this study.

Methods

Chemicals

Gallic acid (98%), metformin and ethylenediaminetetraacetic acid (EDTA) were obtained from Sigma-Aldrich Corp. (St Louis, MO, USA). All chemicals used were of analytical grade quality.

Animals and experimental protocols

Male Sprague-Dawley rats (200–220 g) were obtained from the National Laboratory Animal Center, Mahidol University, Salaya, Nakornpathom. They were housed at 25 ± 2°C with a 12-h dark–light cycle at Northeast Laboratory Animal Center, Khon Kaen University, Khon Kaen, Thailand. All procedures were complied with the standards for the care and use of experimental animals and approved by the Animal Ethics Committee of Khon Kaen University (AEKKU 41/2551). The animals were randomly assigned to 4 groups of 6 rats each: Group I. Control + vehicle (propylene glycol, 0.15 mL/100 g body weight), Group II. HFD + vehicle (propylene glycol, 0.15 mL/100 g body weight), Group III. HFD + gallic acid (20 mg/kg/day) and Group IV. HFD + metformin (100 mg/kg/day).

The animals were fed with HFD for 14 weeks to induce metabolic syndrome while normal control rats were fed with standard normal diet and normal drinking water. HFD contained fructose (60%), casein (20%), fat (5%), cellulose (10%), methionine (0.3%), choline bitartrate (0.2%), minerals (3.5%) and vitamins mix (1%). The composition of HFD followed the method of Suwannaph et al. (Suwannaphet *et al.*, 2010). After 14 weeks of HFD feeding, gallic acid, metformin or vehicle (propylene glycol) were intragastrically administered daily during the last 4 weeks (week 14^{th} - 18^{th}) of the study.

Indirect measurement of blood pressure in conscious rats

Systolic blood pressure (SBP) of all animals was measured weekly using non-invasive tail-cuff plethysmography (IITC/Life Science Instrument model 229 and model 179 amplifiers; Woodland Hills, CA, USA). In brief, conscious rats were placed in a restrainer and allowed to be calm prior to blood pressure measurement. The tail of each rat was placed inside the tail cuff, and the cuff was automatically inflated and released. For each rat, blood pressure was recorded as the mean value from the three measurements with 15 min intervals.

Fasting blood glucose (FBG) and oral glucose tolerance test (OGTT) assessments

Rats were fasted overnight (8-10 h) and blood samples were taken from a lateral tail vein to measure the FBG using a glucometer (Roche Diagnostics Australia Pty. Ltd., Sydney, Australia). Then, the animals were orally administered with glucose at a dose of 2 g/kg body weight in order to determine glucose tolerance. The blood glucose concentration before glucose loading (FBG or 0 min) and at 30 and 120 min after glucose administration was investigated. Area under the curve (AUC) of glucose concentration was calculated from the time curve of blood glucose concentrations over the period of 120 min by using the trapezoidal rule formula (Tai, 1994).

Fasting serum insulin assessments and HOMA-IR calculation

The concentration of insulin in serum was examined using Rat Insulin ELISA Kit (Millipore Corporation, Billerica, MA, USA). HOMA-IR score was expressed as an index of insulin resistance (Matthews *et al.*, 1985) and calculated by the formula HOMA-IR = fasting insulin (U/l) × fasting glucose (mmol/L)/22.5 as described by Guo et al. (Guo *et al.*, 2007).

Assay of total cholesterol and triglyceride

Plasma total cholesterol and triglyceride were investigated by the Clinical Chemistry Laboratory Unit of Faculty of *Associated Medical Sciences*, Khon Kaen University, using the Beckman Synchron LX20 Pro (Holliston, MA, USA). Reagent, Control and Calibrator Kits for total cholesterol and triglyceride were purchased from PCL Holding Co., Ltd. (Bangkok, Thailand).

Statistical analysis

Data are expressed as mean ± standard error of mean (SEM). The differences among treatment groups were analyzed by one-way analysis of variance (ANOVA) with a post-hoc test. A *p*-value of less than 0.05 was considered statistically significant.

Results

Effect of gallic acid and metformin on blood pressure in conscious rats

At the beginning of the study, average baseline values of SBP among all groups of rats were not significantly different (Figure 1). After 18 weeks of HFD feeding, SBP was progressively increased in metabolic syndrome rats compared to those of normal control rats (157.5 ± 2.2 mmHg vs. 117.3 ± 1.8 mmHg) ($p < 0.05$). However, treatment with gallic acid or metformin for 4 weeks significantly attenuated SBP (126.9 ± 2.6 mmHg and 130.0 ± 1.7 mmHg, respectively) in HFD-fed rats compared to untreated HFD-fed rats ($p < 0.05$).

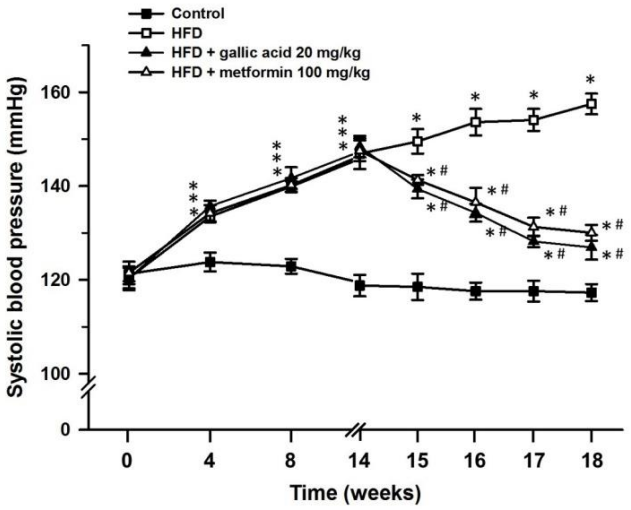

Figure 1 Effect of gallic acid and metformin on systolic blood pressure during 18 weeks of HFD-fed rats. Results are expressed as mean ± SEM. *$p < 0.05$ vs. control group, $^{\#}p < 0.05$ vs. HFD group (n = 6).

Effect of gallic acid and metformin on insulin sensitivity

After 18 weeks of HFD feeding, there were no significant difference in animal body weight between groups (Table 1). Fasting blood glucose, serum insulin concentration and HOMA-IR scores in rats fed with HFD were higher than those of rats fed with a normal diet, indicating insulin resistance in HFD group ($p < 0.05$). The increase in levels of fasting glucose and insulin, and HOMA-IR score were significantly alleviated by gallic acid and metformin treatment ($p < 0.05$) (Table 1). Metformin was found to be more effective in reducing the elevated blood glucose levels and HOMA-IR scores compared to gallic acid ($p < 0.05$).

Table 1 Biochemical parameters and body weight after 18 weeks of HFD-fed rats.

Parameters	Control	HFD	HFD + gallic acid	HFD + metformin
Fasting glucose (mg/dL)	80.5 ± 1.7	121.5 ± 2.1*	100.0±3.9*# †	87.7 ± 3.7#
Fasting insulin (ng/mL)	0.21 ± 0.05	1.34 ± 0.06*	0.41 ± 0.05*#	0.32 ± 0.03#
HOMA-IR score	1.3 ± 0.2	8.5 ± 0.3*	2.5 ± 0.3*# †	1.7 ± 0.2#
Body weight (g)	413.7 ± 10.6	415.3 ± 7.6	422.2 ± 10.7	416.8 ± 4.5

Data are shown as mean ± SME.

*p<0.05 vs. control group, #p<0.05 vs. HFD group, †p<0.05 vs. HFD + metformin group (n = 6).

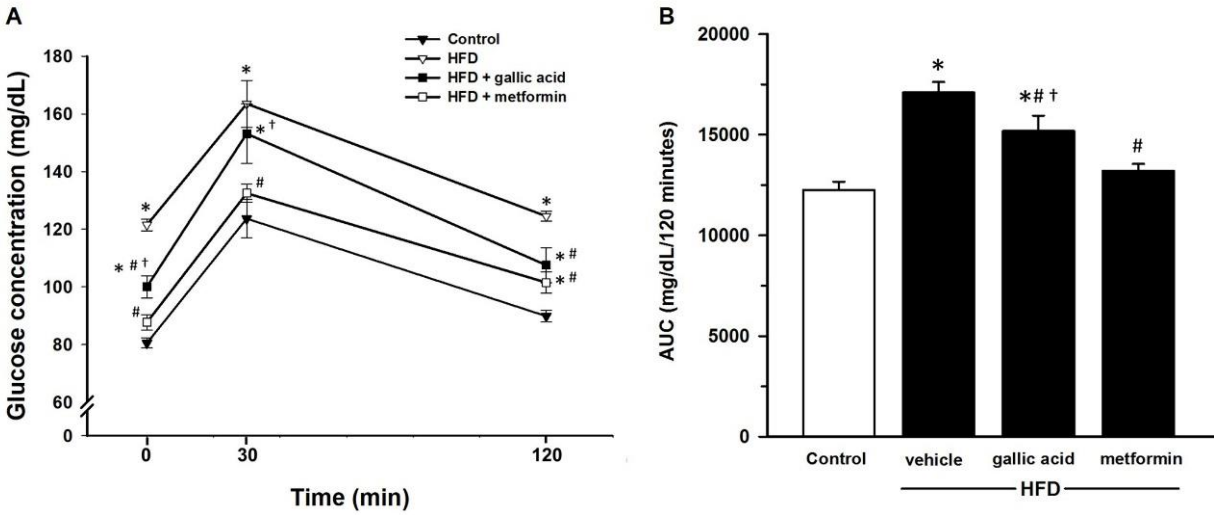

Figure 2 Effect of gallic acid and metformin on (A) oral glucose tolerance test (OGTT) and (B) area under the curve (AUC) of OGTT after 18 weeks of HFD-fed rats. Results are expressed as mean ± SEM. *$p < 0.05$ vs. control group, #$p < 0.05$ vs. HFD group, †p<0.05 vs. HFD + metformin group (n = 6).

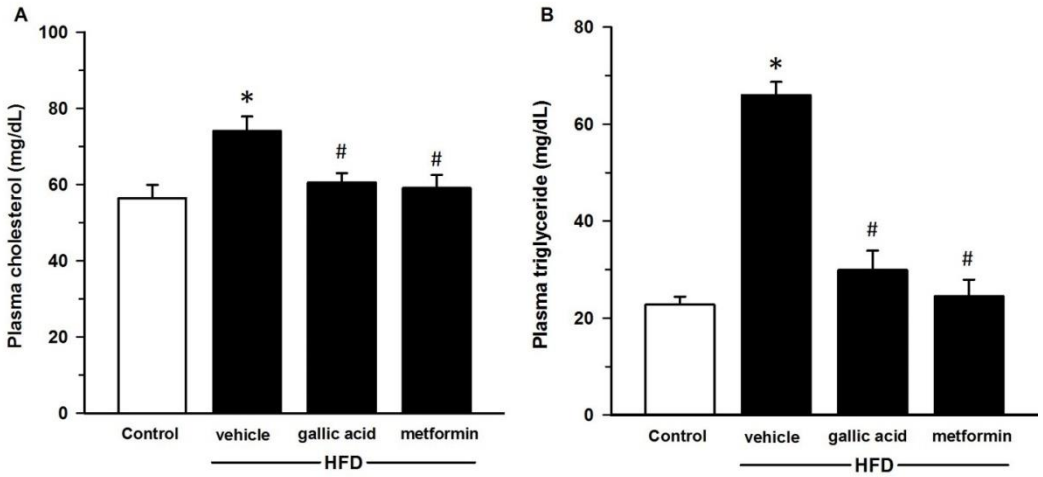

Figure 3 Effect of gallic acid and metformin on plasma (A) cholesterol and (B) triglyceride levels after 18 weeks of HFD-fed rats. Results are expressed as mean ± SEM. *$p < 0.05$ vs. control group, $^{\#}p < 0.05$ vs. HFD group (n = 6).

Effect of gallic acid and metformin on glucose tolerance

Significantly impaired glucose tolerance and increased AUC of glucose concentration during OGTT were found in rats fed with HFD ($p < 0.05$) (Figure 2A and 2B). However, treatment with gallic acid or metformin to rats fed with HFD for four weeks significantly improved glucose tolerance compared to untreated HFD-fed rats ($p < 0.05$). Metformin was found to be more effective in reducing the elevated AUC of glucose concentration during OGTT compared to gallic acid ($p < 0.05$).

Effect of gallic acid and metformin on plasma total cholesterol and triglycerides concentrations

Levels of plasma total cholesterol and triglycerides were significantly elevated in HFD-fed rats compared to those of the control group ($p < 0.05$). Administration of gallic acid or metformin significantly reversed hyperlipidemia by decreasing plasma total cholesterol and triglycerides levels in rats fed with HFD ($p < 0.05$) (Figure 3A and 3B).

Discussion and Conclusion

The present study demonstrates the therapeutic effects of gallic acid on blood pressure, insulin sensitivity, and hyperlipidemia in rats with HFD-induced metabolic syndrome. We found that rats fed with HFD exhibited metabolic syndrome, including, hypertension, insulin resistance, hyperglycemia, and dyslipidemia. Gallic acid and metformin supplementation attenuated hypertension and metabolic abnormalities in metabolic syndrome rats.

We observed that gallic acid reduced blood glucose, serum insulin, AUC of glucose concentration during OGTT, and HOMAR-IR score, indicating that gallic acid improves insulin sensitivity and hyperglycemia in HFD-induced metabolic syndrome rats. Furthermore, gallic acid also reversed dyslipidemia in rats fed with HFD by decreasing plasma cholesterol and triglyceride levels. These results confirm previous study that gallic acid significantly improved glucose tolerance, and decreased concentrations of blood glucose, triglyceride and cholesterol in diabetic rats (Latha and Daisy, 2011). The underlying mechanism of gallic acid improving glucose and lipid metabolic changes in the present study was unclear. It could involve the PI3K/p-Akt signaling pathway since there is evidence that gallic acid alleviated hyperglycemia by enhancing glucose uptake through translocation and activation of GLUT4 in PI3K/p-Akt signaling pathway (Gandhi *et al.*, 2014). In addition, the apparent antihyperlipidemic effect of gallic acid may be linked to its antihyperglycemic effect. It has been reported that hyperglycemia is a major determinant of total cholesterol and triglyceride concentration (Ahmed *et al.*, 2001).

Our results confirm cardiovascular complications in HFD-fed rats, indicating by high blood pressure (Palanisamy and Venkataraman, 2013). We found that gallic acid reduced blood pressure in HFD-induced metabolic syndrome in rats. It is possible that gallic acid decreased blood pressure in HFD-induced metabolic syndrome rats was most likely due to its antioxidative and an angiotensin-converting-enzyme (ACE) inhibitor effect. Previous studies have established the potential antioxidant effect of gallic acid, such as scavenging free radicals and increasing NO availability (Hsu and Yen, 2007; Punithavathi *et al.*, 2011b). In addition, gallic acid clearly reduced blood pressure in spontaneously hypertensive rats and increased NO levels by increasing phosphorylation of eNOS in human umbilical vein endothelial cells (Kang *et al.*, 2015). Gallic acid also suppressed aortic AT1 receptor and ACE1 protein expression resulting in decrease blood pressure in spontaneous hypertensive rat (Jin *et al.*, 2017).

Metformin was used as a positive control in this study. It is a standard antidiabetic drug for treating in hyperglycemia, insulin resistance and metabolic syndrome. Metformin reduces blood glucose, improves insulin sensitivity, and reverses dyslipidemia in HFD-fed rats (Bagul *et al.*, 2012). Additionally, these results are consistent with a recent study that metformin markedly reduced blood pressure and restored endothelial dysfunction in streptozotocin-induced diabetic rats (Majithiya and Balaraman, 2006)

In summary, we have demonstrated that gallic acid reduced blood pressure, improved insulin sensitivity and reversed dyslipidemia in high-fructose diet-induced metabolic syndrome rats. We suggest that gallic acid is a novel promising therapy for the treatment of metabolic syndrome, including hypertension, insulin resistance and dyslipidemia.

Acknowledgements

This work was supported by a grant from Invitation Research Fund, Faculty of Medicine, Khon Kaen University. Sarawoot Bunbupha holds a scholarship from a Postgraduate Scholarship of Faculty of Medicine, Khon Kaen University, Thailand.

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