Restoration of Lung Microvasculature in Diabetic Condition after Curcumin Supplementation

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Objective: *To investigate the effect of curcumin in the restoration of lung microvasculature in streptozotocin-induced diabetic model.*

Material and Method: *Operation of diabetic rat model was induced by streptozotocin (STZ: 60 mg/kg BW). Male rats (7 to 8 weeks old) have been classified into three groups, control (C), diabetic (DM) and diabetic rats supplemented with curcumin (DMC) (200 mg/kg BW). After 8 weeks, lung microvasculature was investigated under vascular corrosion cast technique and examined by scanning electron microscope (SEM).*

Results: *In DM group, structural damages of pulmonary capillary level were obviously severe, defined as microangiopathy. The predominant abnormality of pulmonary capillary revealed destroyed characteristics such as shrinkage, constriction and capillary bed deformity. Furthermore, some destruction was observed at arteriole level whereas destructions of large and small arteries were rarely noticed. Regarding the diameters, the pulmonary capillary of DM group considerably decreased in sizes. Interestingly, upon curcumin supplementation, recovery of pulmonary capillary was predominantly enhanced, demonstrating reformed typical microvasculature pattern. Moreover, the diameter sizes of DMC pulmonary capillary were fully restored forward to normal control condition.*

Conclusion: *Curcumin in diabetic rat could appreciably restored pulmonary microangiopathy at pulmonary capillary toward normal structure. Curcumin might be a novel therapeutic agent in pulmonary microvascular diabetic complications.*

Keywords: *Diabetes mellitus, Curcumin, Lung capillary, Vascular corrosion cast, Scanning electron microscope*

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Diabetic mellitus (DM) is one of the major metabolic disorders, triggering many subsequent diabetic complications worldwide. Microvascular and macrovascular complications are serious circumstances, directing to cardiovascular dysfunction and final destruction of body tissues and functions[1].

Vascular complications of diabetes have been associated with increased oxidative stress, inducing by free radical generation such as reactive oxygen species (ROS). Interestingly, hyperglycemic metabolic alteration on endothelial cells could stimulate lots of ROS generation. As a result, diabetic vascular complications have critically occurred, causing endothelial dysfunction and inflammation. Definitely, diabetic vascular complications of cardiovascular and respiratory systems are seriously related to the causes of morbidity and mortality[2,3].

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Although diabetic lung vasculature is crucially associated with systemic cardiovascular and morbidity rates, the information of pulmonary vascular complications in diabetes is limited. Recently, some reports have explored whether diabetes might be a risk factor for pulmonary diseases, such as pulmonary hypertension, inflammation, pulmonary emphysema, and ventilatory dysfunation[3,4].

In diabetes, destruction and severity of pulmonary vessels presented various degrees and changes. From manifestations of vascular pathology, diabetes and hypoxia could induce pulmonary hypertension by changes of marker pattern. Moreover, lungs of diabetes have been demonstrated pulmonary endothelial dysfunction and infiltration of alveolar macrophages. Diabetes combined with moderate hypoxia could also induce right ventricular hypertrophy[3,4].

Therefore, diabetes can induce and relate to pulmonary vascular abnormalities which are associated with a systemic vascular disease. Since pulmonary vessels have complicated morphological structures relating to essential alveoli gas exchanges, features of

diabetic pulmonary vascular complications in diabetic condition should be of concerned and focused on beneficial treatment in further clinical manifestations.

Curcumin has been widely recommended for traditional medical treatment. Curcumin is a phenolic compound, isolated from the rhizome of turmeric (*Curcuma longa).* Its biological activities have been revealed for many significant biological applications, including anti-oxidation, anti-inflammation, anti-hyperglycemia and anti-carcinogen[5-7]. The efficacy of curcumin has been progressively recommended for treatment of diabetes and associated diabetic complications[8-11].

In this work, the aim was to investigate the efficiency of curcumin as a therapeutic agent to attenuate pulmonary microvasculature complication in diabetic model. The pulmonary microvasculature structures among control, diabetes, and diabetes supplemented with curcumin were respectively studied and compared by vascular corrosion cast/scanning electron microscopy (SEM) techniques[12].

Material and Method

Experimental design of diabetic model

The experimental design was carried on male Wistar rats (200 to 250 g), obtained from National Laboratory Animal Center of Mahidol University. Induction of experimental diabetic condition was performed by intravenous injection of streptozotocin (STZ) (Sigma, St. Louis, MO, USA) (60 mg/kg BW), identified with blood sugar level higher than 250 mg/dl. Three groups of samples were classified: control group (C), diabetic group (DM), and diabetic-supplemented with curcumin (DMC; curcumin 99.99% pure, Sigma, St. Louis, MO, USA) at a dose of 200 mg/kg BW in corn oil diet at 3 ml/kg BW by oral gavage. After 8-week experiment, the pulmonary microvasculatures were performed and investigated by vascular corrosion cast/SEM. The protocol of animal research was followed and supervised by Srinakarinwirot University Medical Center Animal Care Committee (Animal ethic number 2/2557).

Vascular corrosion cast technique

Perfusion of animal blood was performed by injection 500 ml of 0.9% NaCl solution through the left ventricle, allocating into ascending aorta and flowing through the circulatory system. Finally, the blood solution was entirely flushed out from the body vessels at the leaked atrium. Then, Batson's No. 17 plastic mixture was freshly prepared and subsequently infused into blood circulation. The sample models with replaced plastic inside the blood vessels were left at room temperature for 30 minutes and then submerged in hot water (80°C) for 3 hours to accomplish plastic polymerization. After plastic polymerization, the lung organs were isolated, and then were digested and corroded with 10% KOH solution at room temperature for 40 days. Finally, pulmonary vascular casts were rinsed in slow running tap water and cleaned in distilled water to remove the corroded elements[12].

Scanning electron microscopy (SEM)

The replica of pulmonary vascular cast was performed for absolute dry, investigated under stereoscopes, and mounted on a metal stub with double glue tape and carbon paint. The replica of pulmonary vascular cast was then coated with gold particles on sputtering apparatus. Finally, the replica of pulmonary vascular casts was examined under SEM (JEOL JSM-5400) at accelerating voltage of 10 KV.

Statistical analysis

The diameters of pulmonary vessels, including small pulmonary artery, arteiole, and capillary, were measured by using SEMAfore computer software program. Comparisons of diameters of pulmonary vessels were analyzed among C, DM, and DMC groups. Statistical analysis was achieved by using ANOVA followed by Bonferroni test, presenting as mean $\pm$ standard error of the mean (SEM). The value of $p<0.05$ was considered to be statistically significant.

Results

Examinations of the pulmonary vasculatures in diabetes revealed various degrees of severity and morphological changes depending on pulmonary levels. Briefly, interested levels of pulmonary vessels were defined as the followings: large pulmonary vessel, small pulmonary vessel, arterioles, and alveolar capillary. In diabetic conditions, manifestations of destructed pulmonary vasculature were markedly demonstrated at pulmonary capillaries of the alveolar walls. Therefore, pulmonary vasculature deformity and destruction were compared and described among C, DM, and DMC groups, according to the features of four levels of vessels.

Control group: characterization of pulmonary vasculature

In control group, the normal healthy characteristic of pulmonary vasculature was typically

demonstrated, including morphology and levels of branching. Generally, large pulmonary vessel divided into small pulmonary vessels, which further branched to be arterioles (Fig. 1A, B). Finally, lots of arterioles divided to be network of pulmonary capillary surrounding the alveoli (Fig. 1C, D). Definitely, manifestation of histological patterns of pulmonary vasculature revealed smooth surface of straight tube of vessels and capillary network (Fig. 2A-C). In higher magnification, normal characteristic of continuous branching patterns and capillary bed network, including normal diameter size, were clearly illustrated (Fig. 2D).

Diabetic group: characterization of lung vasculature

In DM group, large pulmonary and small pulmonary vessels mostly remained normal structures and pattern of branching (Fig. 3A, B). However, a few arterioles were noticeably observed and presented unhealthy morphologies, including slight shrinkage and twisted portions. In comparison to the control group, destruction of pulmonary capillary networks critically demonstrated unhealthy, destroyed characteristics, identified by recognizable shrinkage, constriction, tortuosity and deformity (Fig. 3C, D). Interestingly, the appearance of pulmonary capillaries dropout and discontinuous capillary networks were also characterized extensively (Fig. 3D).

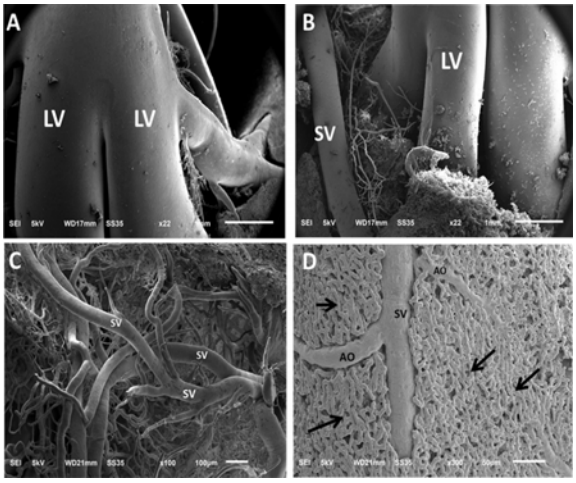

Fig. 1 SEM micrographs of lung vascular cast of control group experiment at low magnification, showing whole blood vessels. A, B) Typical large pulmonary vessel and normal arrangements. C) Healthy typical small pulmonary vessels and branching arrangements respectively. D) Higher magnification of normal descending small vessels, branching-off arteriole, and capillary network. LV = large vessel; SV = small vessel; AO = arteriole, capillary network = arrow.

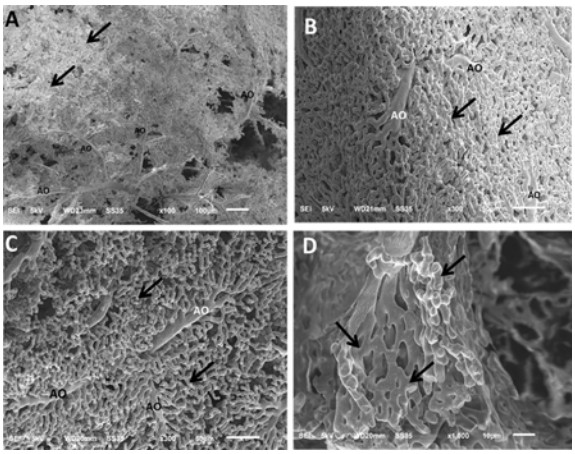

Fig. 2 SEM micrographs of lung vascular cast of control group experiment, showing whole arteriole and capillary network. A) Low magnification of normal arrangements of arteriole and capillary network. B, C) Typical morphology and arrangement of arteriole and capillary network. D) Higher magnification of normal capillary network. AO = arteriole, capillary network = arrow.

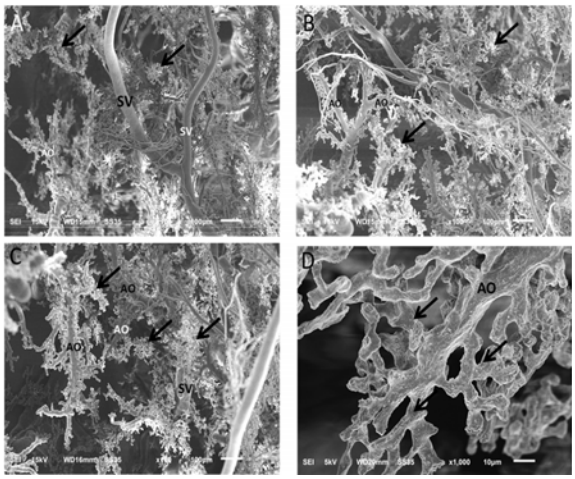

Fig. 3 SEM micrographs of lung vascular cast of diabetic group experiment. A) Presentation of typical small vessel, but of destroyed tortuous arteriole and capillary network. B, C) Destruction and shrinkage and shrinkage of arteriole and capillary network. D) Higher magnification of pulmonary capillaries dropout and destroyed capillary network. SV = small vessel, AO = arteriole, capillary network = arrow.

Diabetic group supplemented with curcumin: characterization of lung vasculature

In DMC group, the architectures of capillary pulmonary network were predominantly recovered and restored, presenting by recovery healthy normal morphology. Typical characteristic of pulmonary capillary and restoration of continuous capillary bed networks were generated and revealed (Fig. 4A-D). The characteristic recovery of pulmonary vasculatures, including arterioles and capillary, were at both morphological structures and branching patterns. The reconstructed interconnection of alveolar capillary network provided evidence that it might be related to normal gas exchanges of alveoli function (Fig. 5A-D).

Comparison of diameters of pulmonary vessels among C, DM, and DMC conditions

According to the comparison of diameters of pulmonary vessels, the average diameters of small artery, arteriole, and capillary of C, DM, and DMC groups are shown in Fig. 6, 7. Regarding the large and small pulmonary arteries, there were no differences in diameters among three groups whereas there was slightly different in average diameters of arterioles. On the contrary, the diameters of pulmonary capillaries were significantly different among three groups. The average diameter of DM pulmonary capillary was decreased in size compared to control group whereas the average diameter of DMC pulmonary capillary was recovered to normal size.

Small pulmonary vessels of three groups still had quite similar diameters; C = 37.663$\pm$1.443, DM = 36.833$\pm$0.463, DMC = 37.500$\pm$0.487. The diameter of arterioles of DM group revealed significantly smaller than that of the C group whereas the size of arterioles of DMC group significantly reverted to the normal value (C=14.460$\pm$1.102, DM = 10.593$\pm$0.428, DMC = 11.486$\pm$0.282). Interestingly, the diameter size of pulmonary capillary of DM group was significantly and obviously decreased when compared to C group (C = 4.445$\pm$0.293, DM = 2.596$\pm$0.061, DMC = 3.292$\pm$0.278). Attractively, after curcumin supplementation, the diameter size of pulmonary capillary of DMC group significantly was restored to normal size. Therefore, these data might verify that curcumin might have an effect in facilitating or recovering the pulmonary vascular vessels, especially microangiopathy, in diabetic animal models.

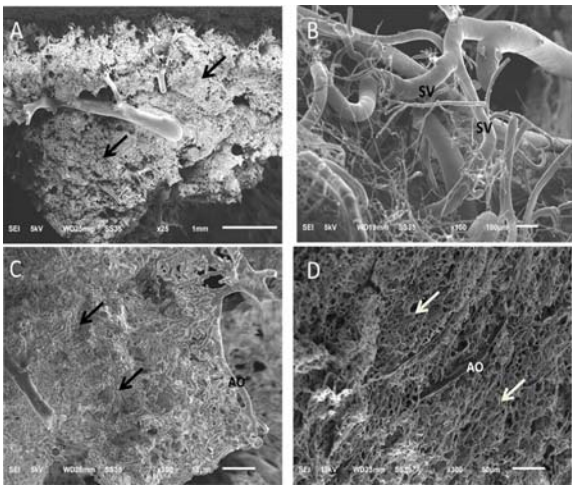

Fig. 4 SEM micrographs of lung vascular cast of diabetic group supplemented with curcumin. A) Reconstruction of pulmonary vessels, especially capillary network. B, C) Presentation of well-defined small vessels. D) Reorganization and recovery of normal arteriole and capillary network. SV = small vessel; AO = arteriole, capillary network = arrow.

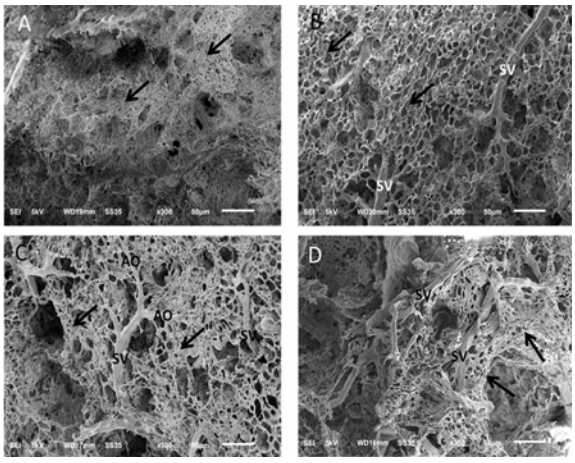

Fig. 5 SEM micrographs of lung vascular cast of diabetic group supplemented with curcumin. A) Reconstruction of pulmonary vessels, especially capillary bed network. B, C) Presentation of reconstructed morphological pattern of especially capillary bed network, shown by higher magnification. D) Reorganization and recovery of normal arteriole and capillary bed network. SV = small vessel; AO = arteriole, capillary network = arrow.

Discussion

In widely-used model, induced-streptozotocin diabetic animals, presented a number of alterations of lung proteins and pulmonary vascular disorders,

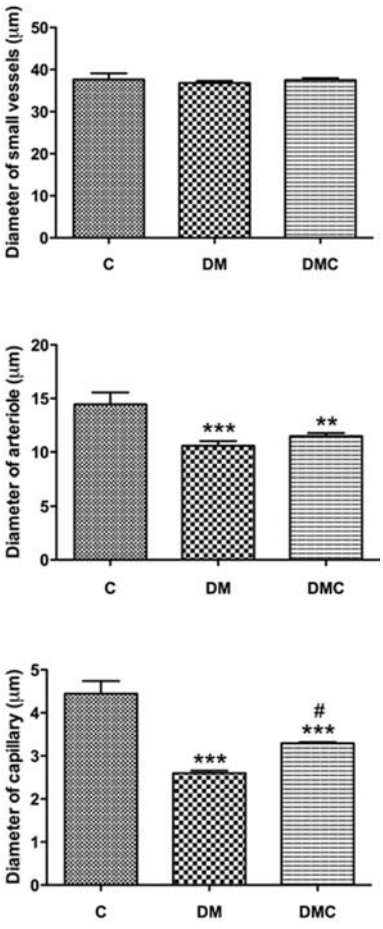

Fig. 6 The average diameters of pulmonary vasculature: small artery (upper panel), arteriole (middle panel), and capillary (lower panel) are demonstrated. The diameters of vessels are compared among control (C), diabetes (DM) and diabetes supplemented with curcumin (DMC). The values are verified as means ± SEM. *** $p<0.001$, ** $p<0.01$, # $p<0.05$.

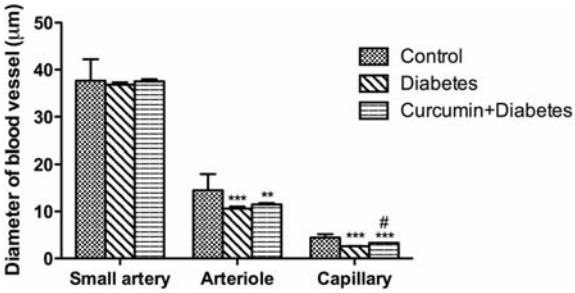

Fig. 7 The comparative diameters of each pulmonary vasculature: small artery, arteriole, and capillary are demonstrated among control (C), diabetes (DM) and diabetes supplemented with curcumin (DMC). The values are verified as means ± SEM. *** $p<0.001$, ** $p<0.01$, # <0.05.

pulmonary hypertension, endothelial dysfunction associated with increased superoxide production, vascular hyper-responsiveness to serotonin[13-16]. In addition, ventricular hypertrophy of the heart has also been reported in the diabetic model[17].

Interestingly, different patterns of pulmonary vascular disease and abnormalities induced by type 1 diabetes have obviously been pronounced and strengthened. The connection between diabetes and pulmonary vascular disease has been confirmed and reliable with a multifactorial pathogenesis, and as part of a systemic vascular disease[3,4]. The abnormalities and changes of pulmonary vasculature were indicated by pulmonary hypertension, such as endothelial dysfunction, downregulation of bone morphogenetic protein receptor type 2 (BMPR2), inflammatory infiltration and response, and pulmonary vascular remodeling.

Our result showed abnormality of pulmonary vasculature, specifically at alveolar capillary network and some parts of arterioles, defined by shrinkage, twisting, and tortuosity. This finding could explain between diabetes and pulmonary vascular disease as previous report[18] and might indicate the possible relation between pulmonary system and cardiovascular system[18,19].

The severity of pulmonary abnormalities occurred at levels of defined vessels, specifically alveolar capillary networks and a few portions of arterioles. These data confirmed that the most severity of destruction of DM pulmonary vessels occurred at pulmonary capillary in term of microangiopathy, demonstrating by both morphology and the size of diameter. Furthermore, the mild destruction might happen at arteriole level. Nevertheless, both pulmonary capillary and arteriole were restored to normal by curcumin.

Generally, pathophysiology of blood vessels in diabetes was considered by many factors, including increased microvascular endothelial cells dysfunction, inflammation, vascular tone, platelet accumulation, and oxidative stress related with the level of nitric oxide[2,18,20-22]. Regarding vascular complications in diabetes, the endothelial dysfunction is a mostly result of the alteration of biological action of nitric oxide (NO).

Many reports have indicated that curcumin had potential treatment for diabetes and its complications due primarily to reduced glycemia and hyperlipidemia. Moreover, lots of literatures have

reported the beneficial potentials and therapeutic applications of curcumin in many diseases and disorders, such as hyperglycemia, adipocyte dysfunction, diabetic-related liver disorder, neuropathy, nephropathy, vascular diseases, pancreatic disorder, and other complications[5,6,23-25]. Interestingly, these studies have indicated and announced that curcumin has important biological antioxidant activities and anti-inflammatory properties, anti-hyperglycemia, anti-hyperlipidemia, anti-tumor, immunomodulation, anti-bacterial, properties.

Curcumin can attenuate diabetes-provoked vascular dysfunction, by inhibiting the activities of cyclooxygenase-2, nuclear factor kappa B, and protein kinase C[6,21,22]. In addition, curcumin improved overstressed vascular contractility, by decreasing the tumor necrosis factor alpha and ROS together with upregulation of heme oxygenase-1 (HO-1) in diabetic rats[23].

Curcumin can reduce the peroxide-associated injury and oxidative damages of blood vessel walls. Based on our results, curcumin induced well-defined attenuation and recovery of pulmonary vessels, especially alveolar capillary network and arterioles. Curcumin might stimulate neovascularization by controlling the balance of production and release of vascular endothelial growth factor, by improvement of antioxidant enzymes in order to perform anti-oxidation property and vascular reactivity. Our previous reports have revealed the effect of curcumin on amelioration of vascular complications in diabetic conditions, such as the vasculature of heart, liver, and choroid of eye[19,26-28]. Therefore, in this experiment, curcumin has further revealed the protective role on reorganization and recovery architectures of pulmonary capillary and arterioles in DMC group.

Conclusion

Curcumin has the potential effect on diabetic pulmonary vascular complication by reconstruction and recovery of dedicated pulmonary capillary networks and arterioles. Its effect may have beneficial use as a novel therapeutic agent for amelioration of diabetes-associated vascular complications. As a result, effect of curcumin on protection and prevention of pulmonary vascular complications in diabetes might be applied for further alternative treatments.

What is already known on this topic?

The association between diabetes and systemic cardiovascular morbidity has been exactly known and recognized. However, very little knowledge about the correlations of diabetes and pulmonary vascular disease has been mentioned. Recent research data revealed that that diabetes might cause pulmonary function changes, such as pulmonary hypertension, inflammation, tissue destruction, and pulmonary artery endothelial dysfunction. Moreover, histopathology of pulmonary vascular complication demonstrated basal lamina thickening and fibrosis. Therefore, the involvement between diabetes and pulmonary vascular disease has been virtually interested.

What this study adds?

This study aims to access the effect of curcumin on pulmonary vascular complication in induced diabetic lung in animal model. In 8-week diabetic conditions, the pulmonary capillary and arteriole are evidently targeted for microangiopathic complication, shown by vascular corrosion cast/SEM. Additionally, after curcumin supplementation, the restoration and amelioration of pulmonary micro-angiopathy have been noticeably demonstrated.

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Potential conflicts of interest

None.

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การฟื้นฟูหลอดเลือดปอดของหนูที่ถูกเหนี่ยวนำให้เป็นเบาหวานภายหลังการได้รับสาร curcumin

วิภาวี อนุพันธ์พิศิษฐ์, หัทยา เพชรพิบูลย์ไทย, พงษ์ศักดิ์ ขันธ์เพ็ชร, รัชฎาภรณ์ ประมงค์

วัตถุประสงค์: เพื่อศึกษาผลของสาร curcumin ในการฟื้นฟูและซ่อมแซมโครงสร้างหลอดเลือดปอดในหนูทดลองที่ถูกเหนี่ยวนำให้เป็นเบาหวานโดยสาร streptozotocin (STZ)

วัสดุและวิธีการ: หนูทดลองเพศผู้ถูกจัดเป็น 3 กลุ่ม อายุ 7 ถึง 8 สัปดาห์ ได้แก่หนูกลุ่มควบคุม กลุ่มถูกเหนี่ยวนำให้เป็นเบาหวานโดยใช้สาร STZ (60 mg/kg BW) และกลุ่มเบาหวานที่ได้รับสาร curcumin (200 mk/kg BW) ทำการทดลองรวมระยะเวลา 8 สัปดาห์ ได้ศึกษาลักษณะโครงสร้างของหลอดเลือดปอดของหนูทั้ง 3 กลุ่มโดยวิธี vascular corrosion cast ร่วมกับกล้องจุลทรรศน์อิเล็กตรอนชนิดส่องกราด

ผลการศึกษา: ศึกษาถึงผลของสาร curcumin ที่มีต่อโครงสร้างหลอดเลือดปอดในภาวะที่ถูกเหนี่ยวนำ ให้เป็นเบาหวานที่ระยะเวลา 8 สัปดาห์ แบ่งหลอดเลือดเป็นสี่ระดับ ได้แก่ large pulmonary, small artery, arteriole, และ pulmonary capillary พบว่าในหนูกลุ่มเบาหวาน หลอดเลือดระดับ pulmonary capillary มีความเสียหายรุนแรงมากที่สุด มีลักษณะเหี่ยวแฟบ คดงอและสูญเสียโครงสร้างประสานแบบร่างแห โครงสร้างของหลอดเลือด arteriole มีความเสียหายเล็กน้อยในขณะที่หลอดเลือด large pulmonary และ small artery ไม่พบความเสียหายจากการวิเคราะห์ขนาดของเส้นผ่าศูนย์กลางของหลอดเลือดในหนูกลุ่มเบาหวาน ยืนยันว่าหลอดเลือดระดับ pulmonary capillary มีค่าน้อยลงมากเมื่อเทียบกับกลุ่มควบคุม แต่ในกลุ่มหนูเบาหวานที่ได้รับสาร curcumin มีการซ่อมแซมและฟื้นฟูสภาพทำให้ขนาดของเส้นผ่าศูนย์กลางของ pulmonary capillary มีค่ามากเพิ่มขึ้นเข้าสู่สภาวะปกติและใกล้เคียงกลุ่มควบคุม ส่วนการเปลี่ยนแปลงขนาดของหลอดเลือดระดับ arteriole มีค่าแตกต่างเล็กน้อยระหว่างสามกลุ่มเท่านั้น ดังนั้นในหนูที่เป็นเบาหวานพยาธิสภาพที่เด่นชัดเกิดขึ้นที่หลอดเลือดขนาดเล็กที่ระดับ pulmonary capillary และ arteriole แต่เมื่อได้รับสาร curcumin พบว่าโครงสร้างหลอดเลือดเหล่านี้มีการซ่อมแซมและฟื้นฟูสภาพเข้าสู่สภาวะปกติและใกล้เคียงกลุ่มควบคุม

สรุป: สาร curcumin สามารถช่วยในการรักษาฟื้นฟูและซ่อมแซมสภาพหลอดเลือดปอดที่เสียหายจากสภาวะเบาหวานโดยเฉพาะพยาธิสภาพของหลอดเลือดขนาดเล็ก ดังนั้นสาร curcumin มีคุณสมบัติที่ดีต่อการลดภาวะแทรกซ้อนของหลอดเลือดปอดในภาวะเบาหวานจึงน่าสนใจที่จะนำไปใช้เป็นประโยชน์ในการพัฒนา ด้านการรักษาโรคเบาหวานต่อไป