Effect of Curcumin on Characterization and Localization of Interleukin-13 and Tumor Necrosis Factor-alpha in Liver of Diabetic Rats

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Objective: *To localize and characterize inflammatory markers: interleukin-13 (IL-13) and Tumor necrosis factor-alpha (TNF-alpha) in recovery livers after curcumin supplementation in streptozotocin-induced diabetic rats.*
Material and Method: *Induced diabetic male rats were achieved by streptozotocin intravenous injection (50 mg/kg BW). The rats were divided into three groups, control rat (C), diabetic rat (DM) and diabetic rat supplemented with curcumin (DMC) (200 mg/kg BW) that has been proposed for anti-inflammation and antioxidant activities. After 12 weeks of curcumin supplementation, liver tissues were collected and processed for hematoxylin & eosin staining and immunohistochemistry. The localization and characterization of IL-13 and TNF-alpha were investigated and compared among three groups in order to analyze the efficiency of curcumin in recovering liver tissues.*
Results: *According DM group, high intensity of IL-13 and TNF-alpha were accumulated around central vein, along hepatic parenchyma, and at perivascular sinusoidal areas. In contrast, the characterization of IL-13 and TNF-alpha in DMC were attenuated. Then, the liver tissues were recovered and engaged by less severity sign of inflammations. Therefore, dietary curcumin might have efficacy to ameliorate diabetic complications in terms of controlling and modulating inflammatory parameters, including IL-13, and TNF-alpha.*
Conclusion: *Administration of curcumin successfully attenuated liver tissue by means of decreased inflammatory cytokine markers. The potential beneficial effects of curcumin have been shown to decline the inflammatory of liver tissue, concerning illustration of IL-13, and TNF-alpha. Therefore, the efficiency and achievement of curcumin might be applied to be an alternative therapeutic agent in diabetic liver.*

Keywords: *Curcumin, Diabetes, Liver injury, IL-13, TNF-alpha, Inflammatory markers*

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Hyperglycemia of diabetes influences and prolongs crucial oxidative environments to cells and tissues. Oxidative stress, induced by free radical generation, plays a critical role in diabetic pathophysiology and complications, including diabetic liver injury[1-4]. However, cellular oxidative damage is also associated with other cellular mechanisms, including cellular inflammation and lipid peroxidation[4-6]. Moreover, cellular inflammation is considered to contribute in diabetic complications[6]. Therefore, cellular inflammatory cytokine markers are interested and studied for many aspect and conditions in diabetes.

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Concerning DM influence on liver, severity of diabetic conditions have been related with liver disease and its complications, including acute liver failure, cardiovascular disease, hepatic encephalopathy[1,3-5]. Consequently, progression of chronic liver disorders is a key role in relation with hyperglycemia condition. It has been suggested that the development of diabetes further responses a higher degree of liver failure[7].

In diabetic condition, increased oxidative stress has been performed through the generation of reactive oxygen species by chronic hyperglycemia and soluble advanced glycated end-products presenting in blood-stream. In addition, these redox changes activate stress response signaling pathways which further induce nuclear factor kappa B (NF-kappa B) and activator protein 1 (AP-1) mediated transcriptional activation of important inflammatory such as tumor necrosis factor (TNF-alpha) and interleukin 6 (IL-6)[8].

Moreover, interleukin 13 (IL-13) has been interested because it is primarily a cytokine that possesses powerful anti-inflammatory properties on development of type 1 diabetes in diabetes-prone non obese diabetic (NOD) mice. It has been suggested that IL-13 treatment might decrease the incidence of spontaneous type 1 diabetes and significantly attenuate insulitis[9].

According to diabetic research, the most commonly diabetic animal models are performed by administration of toxic compounds[10]. Streptozotocin (STZ) and alloxan are effectively used in order to specifically destroy pancreatic beta-cells. As mention previously, liver disorders and complications related with diabetic condition can be generated and performed more severity. As a result, body metabolisms are disturbed and reveal malfunctions because liver is the important organ for metabolism homeostasis. Therefore, there are many studies focusing to prevent and protect liver diseases in diabetic condition[8,11]. It has been shown that curcumin substance can prevent high fat diet which induces insulin resistance and obesity via attenuating lipogenesis in liver and inflammatory pathway[12].

In general, curcumin is the principal compound of turmeric rhizome, which belongs to a member of the ginger family, *Curcuma longa*. Curcumin is an isolated phenolic compound which has potent antioxidant, anti-inflammatory, and anti-carcinogenic activities[8,13]. It has been beneficially used for humanities in many aspects, including food, medicine and cosmetic. Regarding biological and clinical effects, curcumin has been used to treat various diseases such as diabetes, renal lesion, liver disorders, lung injury, atherosclerosis, myocardial infarction, and wound healing[13-15].

Concerning liver injury, curcumin reveals protective effect by enhancing antioxidant enzyme activates, and by inhibition of p53 and mitogen-activating protein kinase mediated stress signals[16]. Moreover, it has potential to diminish macrophage infiltration in induced-diabetic kidney, through inhibition of NF-kappa B transcription factors and proinflammatory cytokines: TNF-alpha and interleukin 1 (IL-1)[17]. In addition, curcumin also controls the expression of many inflammatory enzymes, cytokines, adhesion molecules, and cell survival proteins[13]. As a result, curcumin reveals effective potential on molecular targets at biochemical and molecular levels. Concerning streptozotocin-induced liver injury, curcumin has been proposed to protect liver damages. Nevertheless, there are many reports about curcumin efficiency on TNF-alpha, but only few reports reveal about effect of curcumin on IL-13. Consequently, the comparative effect of curcumin on expression of IL-13 and TNF-alpha in liver diabetes are indeed interested.

Therefore, this study aims to investigate the effect of curcumin on expression of IL-13 and TNF-α in liver tissue in streptozotocin induced diabetic rats. Moreover, anti-inflammatory of curcumin would be focused and supported by this investigation.

Material and Method

Sample model

Six-weeks-old male Wistar rats (weight 200-250 g) were obtained from National Laboratory Animal Center of Mahidol University. The rats were housed under controlled environmental conditions (25$\pm$2°C), kept under a 12-h light/dark cycle and ad libitum access to water and food at Medical Center Animal Care Laboratory, Srinakharinwirot University. All of the animals were supplied access to water and standard rat chow. The experimental procedure were performed in accordance with the instructional guidelines approved by the animal ethic committee of faculty of medicine.

Induction of diabetes

Diabetic rats were induced by a single intravenous injection of streptozotocin (STZ) (50 mg/kg BW: Sigma, St. Louis, MO, USA) dissolved in citrate buffer (0.1 M). Control rats received an injection with citrate buffer alone. After STZ injection, blood sugar levels were determined by one-touch glucometer everyday. Rats having blood sugar level >250 mg/dl were considered and selected as diabetic condition. In addition, streptozotocin (STZ) was used as a toxic diabetogenic agent due to specifically destruction at pancreatic beta cells[18,19]. Therefore, it was extensively used to construct the model of experimental diabetic model.

Animal groups and experimental design

The rats were randomly divided into three groups (10 animals/group):

Group I: Control group (C group): the rats were injected with citrate buffer (0.1 M) alone.

Group II: Diabetic group (DM group): rats were injected with STZ (50 mg/kg BW). If the STZ-induced animals were checked to have diabetic condition, they would be classified into DM group. Then, DM group would be daily fed only corn oil diet 3 ml/kg BW by intragastric feeding.

Group III: Diabetic rats supplemented with curcumin (DMC group): the diabetic rats were received

daily fed corn oil diet 3 ml/kg BW containing curcumin 200 mg/kg BW by intragastric feeding (curcumin 99.99% pure, Sigma, St. Louis, MO, USA).

In experimental design, three groups of rats were observed and investigated up to 12 weeks. At the final point of 12 weeks, the rats of each groups were intensely anesthetized and quickly surgical terminated. The antero-medial lobes of liver were removed and fixed in 4% paraformaldehyde for histological and immunohistochemical studies under light microscope (Olympus light microscope (BX-50, Olympus, Japan).

Immunohistochemistry for IL-13 and TNF-alpha

The preparations of liver tissues of three groups were performed by the same procedure as mentioned above. The liver tissue were embedded in paraffin, then prepared as 5 μm thick tissue sections using microtome. The tissue sections were mounted onto positive charge coated glass slides used for immunohistochemical staining. After deparaffinization with xylene and rehydration in graded ethanol series, the tissue slides were washed in distilled water (dH_2O). Regarding antigen retrieval, the slides were immersed in citric acid buffer (pH 6.0) at 70°C for 10 min, cooled to room temperature and washed in distilled water (dH_2O). The endogenous peroxidase activity was blocked with 0.6% hydrogen peroxide in 0.1M phosphate-buffered saline (PBS) for 10 minutes at room temperature, then washed in distilled water (dH_2O) and PBS-Tween (PBS-T) respectively. The sections were then incubated with 5% Bovine serum albumin (BSA) for 30 min at room temperature.

After removing 5% BSA without washing, the tissue sections were incubated with primary antibodies that were monoclonal anti IL-13 and anti-TNF-alpha antibodies overnight at 4°C. The primary antibodies: anti-interleukin-13 and anti-tumor necrosis factor alpha were purchased from Santa Cruz Biotechnology Inc., and Abnova Inc., CA, USA. The dilutions of both primary antibodies were performed at 1: 50 and incubated at 4°C overnight.

Tissue sections were washed by PBS-T, incubated with biotinylated secondary antibody that was horseradish peroxidase (HRP)-conjugated secondary antibody at room temperature for 1 h. Then, the antigen signals were amplified by using Avidin-Biotin complex system (SC-2023, Santa Cruz Biotechnology Inc., Santa Cruz, CA, USA). Then the tissue sections were washed in PBS-T and were detected by using diaminobenzidine tetrahydrochloride (DAB) substrate (34065, Peirce, USA). The tissue sections were then counter stained with Mayer's hematoxylin, rinsed with deionized water, dehydrated through a series of graded ethanol and xylene respectively, covered with permount, followed by glass cover slip, examined and photographed by Olympus light microscope (BX-50, Olympus, Japan). The intensity of immunohistochemistry was visualized and scored by the potent marker of brown-colored product at areas of antigen and peroxidase-conjugated antibody complexs. Negative control sections were performed under identical procedure with the buffer solution substituting for the primary antibody.

Results

Characterization and localization of IL-13 immunoreactivity in the diabetic liver tissues after curcumin supplementation

Immunological presentation of IL-13 in liver tissues of control groups at 12 weeks were rarely demonstrated and characterized by very weak brownish intensity (Fig. 1A, 1D, 2A, 2D). However, in diabetic groups, immunological localization and characterization of IL-13 were demonstrated as a large number of accumulations and deposition of IL-13 around cellular central vein, especially at the innermost cell layer surrounding central vein (Fig. 1B, 1E). It might be suggested that hepatic stellate cell (HSC cell) were activated and functioned to respond in order to protect liver cell damages. Moreover, the brownish color of IL-13 was also revealed along hepatic plate, at hepatic sinusoidal areas (Fig. 2B, 2E). The brownish intensity of IL-13 demonstrated in diabetic group were distributed and localized more than in control group respectively.

Interestingly, the inflammatory marker of IL-13 was dramatically reduced in its intensity in diabetic group supplemented with curcumin. Hepatic cells around central veins showed marked reduction of inflammatory marker of IL-13 (Fig. 1C, 1F). Only some spots of IL-13 were scatter along central vein and at hepatic sinusoidal area (Fig. 1C, 1F, 2C, 2F). The attenuation and recovery of hepatic parenchyma were exhibited closely similar to the control groups.

Characterization and localization of TNF-alpha immunoreactivity in the diabetic liver tissues after curcumin supplementation

Localization and characterization of inflammatory cytokine marker TNF-alpha were compared among three groups of control, diabetes and diabetes supplemented with curcumin. Regarding control groups, localized TNF-alpha immunological

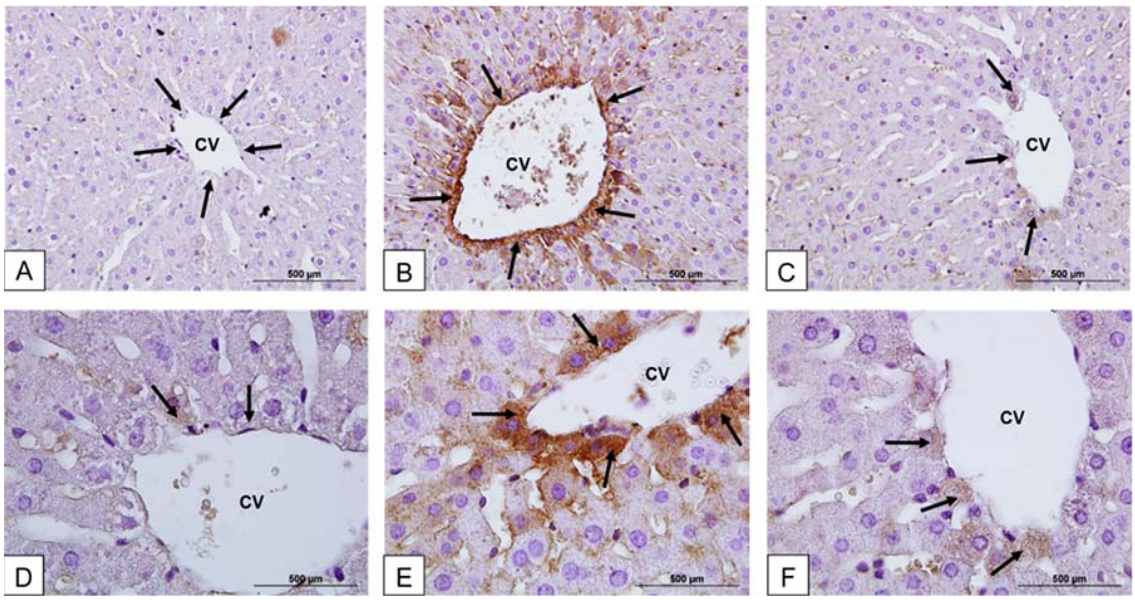

Fig. 1 Micrographs of IL-13 appearance around cellular layer of central vein of liver tissue at 12 weeks, by immunohistochemical staining. C group: ($1A^{+}$ and $1D^{++}$) shows characterization of typical central vein without intensity of IL-13 (arrow). DM group: ($1B^{+}$ and $1E^{++}$) The appearance of IL-13 accumulation at cellular layer of central vein is revealed by dominantly increased brownish intensity (arrow). DMC group: ($1C^{+}$ and $1F^{++}$) Cellular tissue of central vein presents the reduction of IL-13 accumulation (arrow). $^{+}$ 40X magnification; $^{++}$ 100X magnification; CV = central vein.

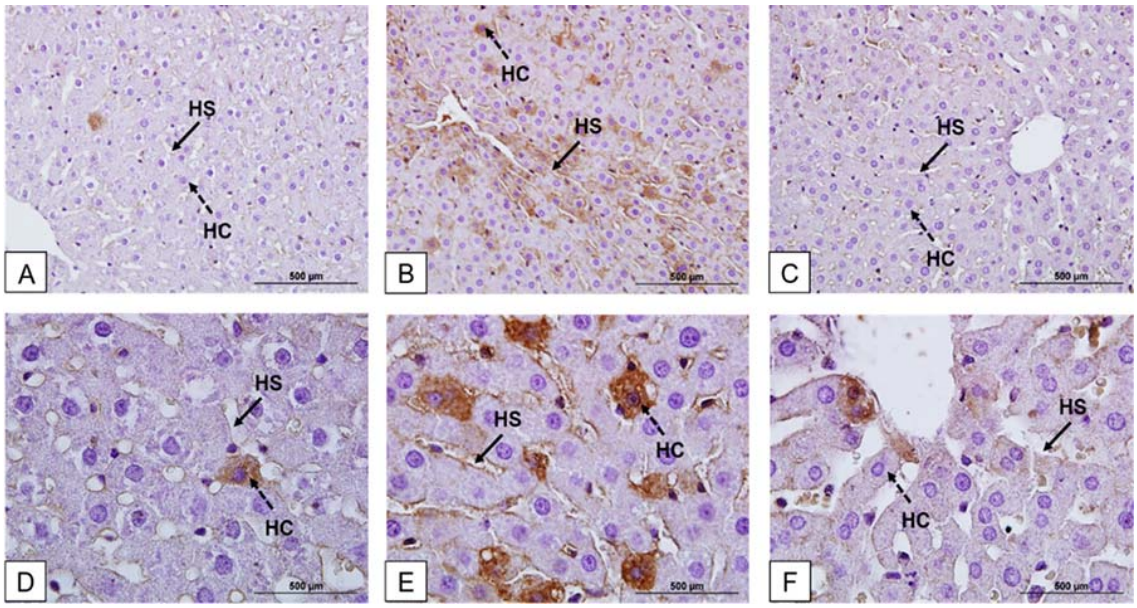

Fig. 2 Micrographs of IL-13 appearance in perisinusoidal space of liver tissue at 12 weeks, by immunohistochemical staining. C group: ($2A^{+}$ and $2D^{++}$) Characterization of hepatic sinusoids situated between hepatocyte plates presents very weak brownish color (arrow). DM group: ($2B^{+}$ and $2E^{++}$) Appearance of brownish intensity of IL-13 along hepatic sinusoidal areas is demonstrated. DMC group: ($2C^{+}$ and $2F^{++}$) Hepatic sinusoidal areas present decreased brownish color of IL-13, compared with DM group. $^{+}$40X magnification; $^{++}$100X magnification; HS = Hepatic sinusoid (dark arrow); HC = Hepatocyte (dashed arrow).

activity were hardly investigated in hepatic parenchyma. The weak signals of TNF-alpha were demonstrated around central vein. (Fig. 3A, 3D) and no signals along perivascular sinusoidal areas (Fig. 4A, 4D). In contrast, for diabetic group, TNF-alpha was intensively demonstrated, presenting by strong brownish color at innermost cell layer around central vein (Fig. 3B, 3E) and also along hepatic cell plate, specifically at perivascular sinusoidal areas (Fig. 4B, 4E). TNF-alpha accumulation in diabetic liver tissue was demonstrated higher intensity compared with normal control group. Therefore, liver tissue of diabetic group showed sign of more severity of inflammation all over the liver tissue compared with the control one, demonstrating by stronger TNF-intensity.

After supplementation of curcumin in DMC groups, the immunological intensity of TNF-alpha brownish color was decreased in liver tissues (Fig. 3C, 3F, 4C, 4F). However, spots of TNF-alpha immunoreactivity were still presented especially at the areas around central veins (Fig. 3C, 3F). Additionally, the sign of inflammation was attenuated in curcumin-treated group, showing by decreased accumulation of TNF-alpha along liver tissues.

Discussion

According to liver injury, some reports suggested about important cells that may take responsibility for means of liver fibrogenesis and liver fibrosis. The key cell is hepatic stellate cell, which can be triggered to be activated cell to produce large amounts of collagen. Hepatic stellate cells are stimulated by other cells, including hepatocyte, T-lymphocyte, and Kuffer cells. The system of stimulation are groups of cytokine and inflammatory secretions such as transforming growth factor beta (TGF-beta), TNF-alpha, insulin-like growth factor (IGF), IL-6, and interferon gamma (INF-gamma), etc[18,19].

Disturbance of liver fibrogenesis condition usually lead to in morphological and pathological changes of intrahepatic parenchyma. Concerning chronic inflammations, chronic necrosis and fibrosis, the increased density of collagen accumulation occurs[20]. Additionally, type II diabetes associated with hyperleptinemia could involve in liver fibrosis. Regarding chronic liver injury, liver fibrogenesis would take action in response as wound-healing process. Remarkably, curcumin could improve liver tissue destruction by inhibiting the proliferation of activated hepatic stellate cells. Because of many potential biological activities of curcumin, it has been proposed to beneficial use for liver fibrosis's prevention and treatment[13].

The increase of inflammatory cytokine in liver tissue of DM suggested that chronic hyperglycemia might stimulate inflammation by increased production of pro-inflammatory such as TNF-alpha, IL-1, IL-6. As a result, NF-kappa B might be over activated in hepatocytes leading to liver inflammation[8,13,16]. Then, T helper 2 cell (Th2 cell) were activated in order to produce IL-13 which suppressed production of pro-inflammatory cytokines, inhibited NF-kappa B function and involved in the role of liver fibrogenesis[21].

Concerning this work, the interested inflammatory cytokine markers are about IL-13 and TNF-alpha. The benefit of curcumin on diabetes may be due to its ability to limit the release of pro-inflammatory factors, by restoring transmembrane potential and stiffening membrane fluidity[8,13,22]. The effects of curcumin have been shown to interact with many cell signaling molecules. Its ameliorative actions play roles on the control and modulation of these molecules, including pro-inflammatory cytokine.

The anti- inflammatory action of curcumin controls and modulates the actions of T- and B-lymphocytes and macrophages by inhibiting proliferation, antibody production (IgG), and lymphokine secretion (IL-4, IL-1, IL-6, and TNF-alpha). In addition, in STZ-induced diabetic rats, the blood levels of IL-6 and TNF-alpha were significantly demonstrated[8,13]. About macrophage modulation, curcumin also suppressed macrophage activities by interacting with macrophage infiltration and preventing pro-inflammatory cytokines release in high glucose condition and in diabetic condition[17,23]. At molecular level, curcumin was competent to interact with many important molecules involved in inflammation. Anti-inflammatory of curcumin is regarded to modulate the inflammatory responses by inhibition the production and expressions of interleukins (IL-1, IL-2, IL-6, IL-8), TNF-alpha, monocyte chemoattractant protein (MCP), migration inhibitory protein; by down regulation of lipoxygenase, inducible nitric oxide synthase (iNOS) enzymes, and cyclooxygenase-2 (COX-2)[8,13,22-24]. The inhibitory effect of curcumin on inflammatory cytokines is proposed via blocking cytokine gene expression by activation of transcription factors NF-kappa B and activating protein-1 (AP-1) and by decrease expression of intercellular signaling proteins[24].

In the present study, the anti-inflammatory

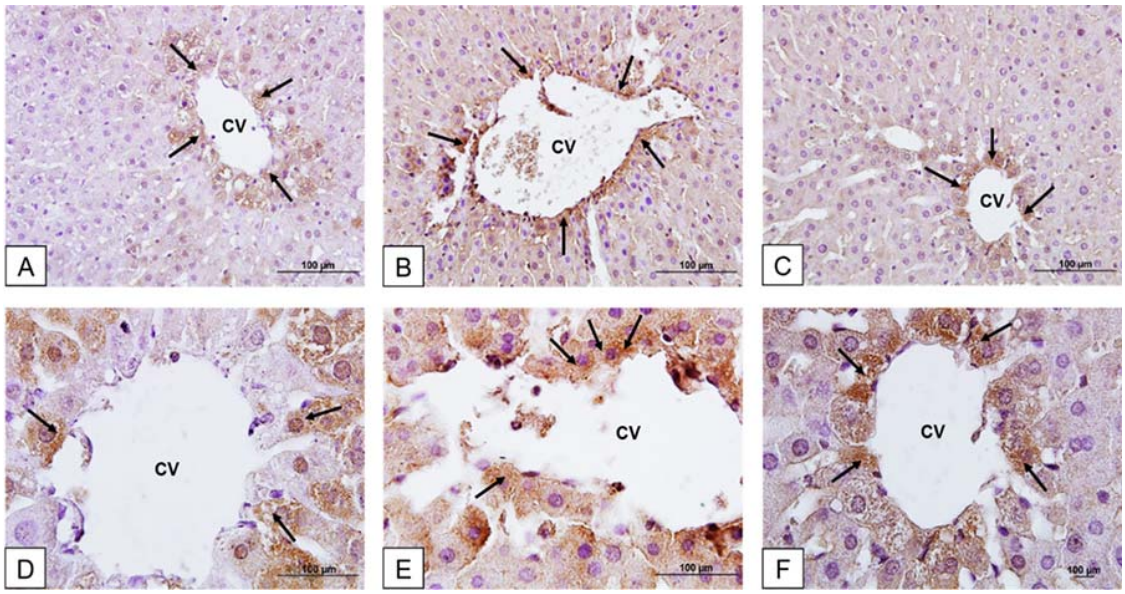

Fig. 3 Micrographs of inflammatory cytokine marker TNF-alpha accumulation in hepatic parenchyma of liver tissue at 12 weeks, by immunohistochemical staining. C group: ($3A^{+}$ and $3D^{++}$) Characterization of TNF-alpha (arrow) is presented in hepatic parenchyma, especially around central vein with very weak brownish color. DM group: ($3B^{+}$ and $3E^{++}$) Intensity of TNF-alpha (arrow) is prominently distributed by strong brownish color at innermost cell layer around central vein. DMC group: ($3C^{+}$ and $3F^{++}$) The intensity of brownish color of TNF-alpha (arrow) is decreased in hepatic parenchyma, compared with DM group. $^{+}$40X magnification; $^{++}$100X magnification; CV = central vein.

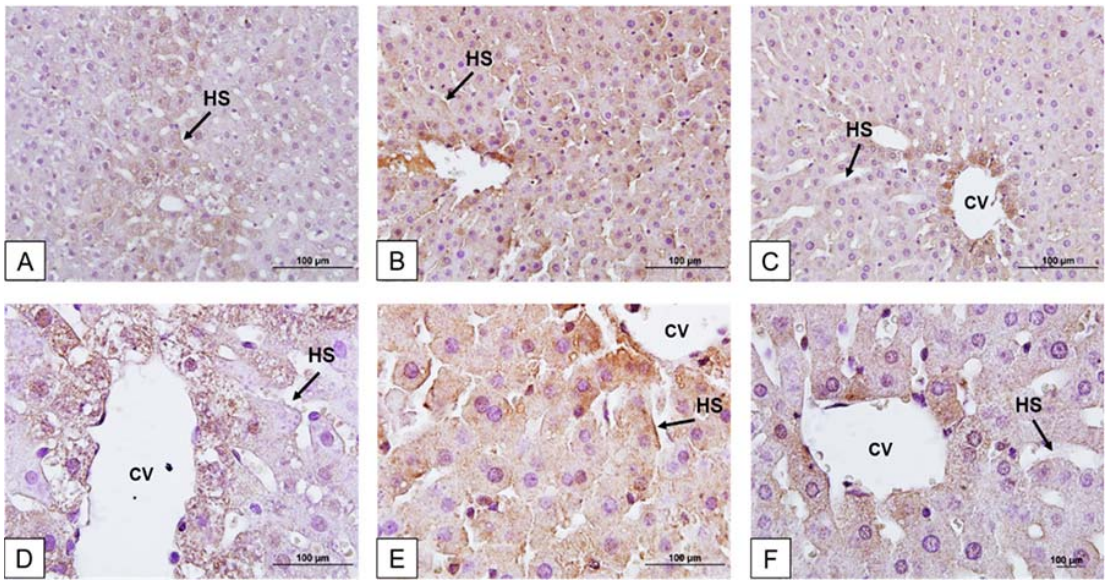

Fig. 4 Micrographs of TNF-alpha distribution in perisinusoidal space of liver tissue at 12 weeks, stained by immunohistochemical staining. C group ($4A^{+}$ and $4D^{++}$) Characterization of hepatic sinusoid presents very weak brownish color of TNF-alpha (arrow). DM group: ($4B^{+}$ and $4E^{++}$) Strong brownish intensity of TNF-alpha distributes as stripes along at hepatic sinusoid (arrow). DMC group: ($4C^{+}$ and $4F^{++}$) Decreased intensity of TNF-alpha is distributed along hepatic sinusoid (arrow). $^{+}$40X magnification; $^{++}$100X magnification; HS = Hepatic sinusoid; CV = central vein.

effect of curcumin revealed in liver tissues, by reducing the localization of IL-13, and TNF-alpha compared with the diabetic livers. In addition, the curcumin effect on IL-13 production and secretion have not been studied and revealed in diabetic condition. Curcumin supplementation considerably improved the liver tissues by preventing pro-inflammatory cytokines releases. Therefore, dietary curcumin might has efficacy to ameliorate diabetic complications in terms of controlling and modulating many inflammatory parameters, including IL-13, and TNF-alpha.

Curcumin has been proposed for its therapeutic activities associating with suppression of inflammation, angiogenesis, tumorigenesis, and diabetes. It also enhances curative effects in wound healing, liver protection, cardiovascular, pulmonary and neurological diseases[8,13,25,26]. Generally, these effects can be attributed to the antioxidant, anti-inflammatory and anticancer activities of curcumin. Moreover, curcumin is an effective scavenger of reactive oxygen species and reactive nitrogen species[8,13,22-27]. Curcumin's protective function is against peroxidative damage of biomembranes, known to be a free-radical-mediated chain reaction. Its function has mainly been attributed to the scavenging of the reactive free radicals involved in peroxidation. These scavenging properties of curcumin have also been considered to be responsible for its protective role against oxidative damage of DNA and proteins which are believed to be associated with a variety of chronic diseases such as cancer, atherosclerosis, neurodegenerative diseases and aging.

Conclusion

The anti-inflammatory effect of curcumin plays important role by modulating the production and expression of inflammatory cytokines: IL-13, and TNF-alpha in diabetic liver tissues. Curcumin supplementation decreases these cytokine markers to protect diabetic liver. The efficiency and achievement of curcumin might be applied to be an alternative novel therapeutic agent in diabetic hepatic pathology.

What is already known on this topic?

According to liver injury and liver complications in diabetes, inflammation and tissue destruction have been reported, relating to many inflammatory cytokines, cellular and tissue responses. Interestingly, the immune response system is widely focused on many cytokine and inflammatory secretions such as transforming growth factor beta (TGF-beta), tumor necrosis factor alpha (TNF-alpha), insulin-like growth factor (IGF), interleukin 6 (IL-6), interferon (INF), etc. However, there are some other inflammatory markers that have not been focused.

What this study adds?

In the present study, characterization and localization of other two inflammatory cytokines: IL-13 and TNF-alpha in induced diabetic condition have been revealed. Moreover, the anti-inflammatory effect of curcumin has been proposed in diabetic liver tissues, by reducing the localization and accumulation of IL-13, and TNF-alpha compared with the untreated-diabetic livers. In addition, curcumin supplementation considerably improved and repaired the diabetic liver tissues by effecting on pro-inflammatory cytokines releases. Therefore, dietary curcumin might have efficacy to ameliorate diabetic complications in terms of controlling and modulating inflammatory cytokines, including IL-13, and TNF-alpha.

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Potential conflicts of interest

None.

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ผลของ Curcumin ต่อการแสดงออกและตำแหน่งของ Interleukin-13 และ Tumor Necrosis Factor-alpha ในตับของหนูที่เป็นเบาหวาน

กมลวัลย์ สถิน, หัทยา เพชรพิบูลย์ไทย, วิภาวี อนุพันธ์พิศิษฐ์

วัตถุประสงค์: เพื่อศึกษาผลของสาร curcumin ต่อการแสดงออกและตำแหน่งของ Interleukin-13 (IL-13) และ Tumor Necrosis Factor-alpha (TNF-alpha) และการฟื้นฟูของเนื้อเยื่อตับในหนูที่ถูกเหนี่ยวนำให้เป็นเบาหวานโดยสาร streptozotocin (STZ)

วัสดุและวิธีการ: หนูเพศผู้ถูกเหนี่ยวนำให้เป็นเบาหวานโดยการฉีดสาร STZ เข้าหลอดเลือดดำ (50 mg/kg BW) และแบ่งหนูออกเป็น 3 กลุ่ม ได้แก่ หนูกลุ่มควบคุม หนูกลุ่มเบาหวาน และหนูกลุ่มเบาหวานที่ได้รับสาร curcumin (200 mg/kg BW) ซึ่งมีคุณสมบัติ anti-inflammation and antioxidant activities หลังจากได้รับสาร curcumin เป็นเวลา 12 สัปดาห์ ได้ศึกษาลักษณะการอักเสบ โดยเน้นศึกษาการแสดงออกและตำแหน่งของสาร IL-13 และ TNF-alpha ในเนื้อเยื่อตับของหนูทั้ง 3 กลุ่ม เพื่อวิเคราะห์ประสิทธิภาพของ curcumin ในการฟื้นฟูของเนื้อเยื่อตับโดยวิธี immunohistochemistry

ผลการศึกษา: หนูกลุ่มเบาหวานมีการสร้างและสะสมของ IL-13 และ TNF-alpha เป็นจำนวนมากที่บริเวณ central veins, hepatic parenchyma และ perivascular sinusoidal area แต่ในหนูกลุ่มเบาหวานที่ได้รับสาร curcumin พบว่ามีการลดลงของสาร IL-13 และ TNF-alpha ซึ่งมีความสัมพันธ์กับการลดการอักเสบของเนื้อเยื่อตับดังนั้น curcumin มีผลในการฟื้นฟูเนื้อเยื่อตับที่ถูกเหนี่ยวนำให้เป็นเบาหวานในแง่ของการควบคุมและลดการอักเสบ โดยมีผลต่อการสร้างและสะสมสาร IL-13 และ TNF-alpha ผลของ curcumin ทำให้เนื้อเยื่อตับที่เป็นเบาหวานมีการเปลี่ยนแปลงในทางที่ดีขึ้นโดยการลด inflammatory cytokine markers

สรุป: สาร curcumin มีบทบาทในการลดการอักเสบในเนื้อเยื่อตับที่มีภาวะเบาหวาน โดยมีผลต่อการสร้างและสะสมของ inflammatory cytokine markers: IL-13 และ TNF-alpha ดังนั้นด้วยประสิทธิภาพของ curcumin จึงอาจนำไปประยุกต์ใช้ในการรักษาหรือป้องกันโรคตับในผู้ป่วยเบาหวานต่อไป