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Research Article

The Effect of Turmeric and Mangosteen Peel Extract on PPARa Gene Expression in the Retina of HFD-Induced Rat Model

Pengaruh Ekstrak Kunyit dan Kulit Manggis terhadap Ekspresi Gen PPARα pada Retina Model Tikus yang Dinduksi DTL

Yenny Noor[1], Diana K Jasaputra[2*], Julia W Gunadi[3], Ronny Lesmana[4,5], Riska A Safira[6]

[1]Department of Opthalmology, Faculty of Medicine, Universitas Kristen Maranatha
[2]Department of Pharmacology, Faculty of Medicine, Universitas Kristen Maranatha
[3]Department of Physiology, Faculty of Medicine, Universitas Kristen Maranatha
[4]Physiology Division, Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran
[5]Physiology Molecular Laboratory, Biological Activity Division, Central Laboratory, Universitas Padjadjaran
[6]Faculty of Medicine, Universitas Kristen Maranatha
Universitas Kristen Maranatha, Jl. Prof. dr. Surya Sumantri, M.P.H. No. 65, Bandung-40164, Jawa Barat, Indonesia
Universitas Padjadjaran, Jl. Raya Bandung Sumedang Km 21, Jatinangor-40161, Jawa Barat, Indonesia
**Corresponding author*
Email: dianakjasaputra67@gmail.com

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Abstract

A long-term high-fat diet (HFD) was proven to induce metabolic dysfunction and causes various organ inflammation, including the retina. As the regulator of lipid metabolism, PPARα plays a role in retinal lipid metabolism and served as one of the targets for decreasing lipid deposition in the retina. Turmeric and mangosteen peel are Indonesian medicinal herbs with enormous health effects, including antiinflammation and hypolipidemic properties. This study aims to determine the effect of ethanol extract from turmeric and mangosteen peel on PPARα gene expression in the retina of an HFD-induced rat model. Twenty male Wistar rats were divided into 5 groups: negative control, positive control, turmeric, mangosteen, and fibrate. At the end of the study, total cholesterol and triglyceride levels from the blood were measured. The retina was extracted to conduct Realtime PCR for PPARα gene expression. The result showed a significant difference in triglyceride levels between positive control and turmeric groups, and PPARα gene expression in the retina between the control negative, positive, and turmeric groups, but no significant difference was found in other groups. This study concludes that the extract of turmeric increases the expression of the PPARα gene expression in the retina in an HFD-induced rat model.

Keywords*: retina; PPARα; HFD; metabolic dysfunction*

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Abstrak

Diet tinggi lemak (DTL) dalam rentang waktu lama telah terbukti menginduksi disfungsi metabolik dan menyebabkan inflamasi berbagai organ, termasuk retina. Sebagai regulator metabolisme lipid, PPARα memegang peran penting dalam metabolisme lipid dan berperan sebagai salah satu target penurunan deposisi lipid di retina. Kunyit dan kulit manggis merupakan obat tradisional Indonesia dengan efek Kesehatan yang luas, termasuk berkhasiat sebagai anti-inflamasi dan hipolipidemik. Penelitian ini bertujuan untuk mengetahui pengaruh ekstrak etanol kunyit dan kulit manggis terhadap ekspresi gen PPARα pada retina tikus model yang diinduksi DTL. Dua puluh ekor tikus Wistar Jantan dibagi menjadi 5 kelompok, yaitu kelompok kontrol negatif, kontrol positif, kunyit, manggis, dan fibrat. Pada akhir penelitian, kadar kolesterol total dan trigliserida dari darah diukur. Retina diekstraksi untuk dilakukan pemeriksaan PCR *realtime* untuk pemeriksaan ekspresi gen PPARα. Hasil penelitian menunjukkan adanya perbedaan bermakna ekspresi kadar trigliserida antara kelompok kontrol positif dan kunyit, dan gen PPARα pada retina antara kelompok kontrol negatif, positif, dan kunyit, namun tidak ditemukan perbedaan bermakna pada kelompok lainnya. Penelitian ini menyimpulkan bahwa ekstrak kunyit meningkatkan ekspresi gen PPARα pada retina tikus model induksi DTL.

Kata kunci: retina; PPARα; DTL; disfungsi metabolik

Introduction

Obesity caused by a high-fat diet (HFD) has increasingly become a global health problem.[1] In 2016, 27.5% of adults were categorized as obese globally, and this estimation increased every year, including in Indonesia.[2,3] Based on Riskesdas (Basic Health Survey), the prevalence of obesity in Indonesia among adults was increasing from 10.5% to 21.8% in 2007 to 2018, respectively.[4] A study by Ayuningtyas et al, showed socioeconomic and geographic disparities among obese adults from 514 districts in Indonesia, Java and Bali had higher obesity prevalence than Papua, Nusa Tenggara, and Maluku.[2] Overall obesity among adults was found 19%, with prevalence in females (25.6%) higher than in males (12.8%).[2]

Obesity is associated with various risks of disease, such as diabetes, heart disease, dyslipidemia, non-alcoholic fatty liver, and other diseases.[1,5] Dyslipidemia is mainly characterized by the increase of triglyceride (TG), which cause other lipid imbalance that finally delays the clearance of lipoprotein with high TG and increases LDL formation.[6] Metabolic dysfunction and dyslipidemia also contribute to metabolic abnormalities in the eye, especially the retina.[7,8] The retina contains a large number of lipids, therefore the consumption of high lipids in diet modulates the lipid composition in the retina.[8] One of the molecular targets for preventing and treating retinal disease caused by lipid deposition is a transcription factor named

Research Article

PPARα (Peroxisome proliferator-activated receptor-alpha), which contributes to retinal lipid metabolism.[7,9]

PPARs are transcription factors expressed in various tissues, consisting of several isoforms, namely PPARα, PPARγ, PPARβ/δ.[10] PPARs are activated when they bind to endogenous ligands such as fatty acids.[11] Once activated, PPARs will undergo heterodimerization with the RXR (Retinoid X Receptor) and form a functional transcriptional unit. PPARs-RXR heterodimers then attach to PPAR Response Elements (PPREs) then stimulate the expression of genes that regulate lipid metabolism.[11] PPARα has a role in controlling lipoprotein lipase expression as well as triglyceride metabolism.[9,12] PPARα also indirectly interacts with nuclear factor (NF)-kB, thus resulting in an anti-inflammatory effect.[11,13] Therefore, PPARα can be used as a therapeutic implication against various diseases. Studies have proven that ethanol extract of curcumin and mangosteen has anti-obesity effects and modulates biochemical and histopathology changes in liver and kidney, respectively.[14,15]

Curcuma longa is a plant that mostly used for many purposes such as for cooking, food coloring, and for traditional chinese medicine.[16] One of Asian country, Indonesia, is one of the countries that uses herbal ingredients such as turmeric and mangosteen for the management of metabolic disorder caused by HFD.[17] Recent studies have shown that 50% ethanol extract from fermented *Curcuma longa* (FCE50) plays a role in lipid metabolism.[14] Research also showed *Curcuma longa* have potentially reduce vascular leakage, suppressed TNFα expression and ROS production on retina via inhibition of Nf-KB.[18,19]

Mangosteen, *Garcinia mangostana*, is a plant that is widely grown in countries in Southeast Asia such as Indonesia, Malaysia and Thailand.[15] Mangosteen peel extract with its α-mangostin content, has a high antioxidant content so that it plays a role in protecting the retina from oxidative stress.[20] Research showed that metabolite compound of *Garcinia mangostana*, γ-Mangostin (xantone derivate) in high fat diet-induced obese rats have PPARα agonist activity and contribute to lipid metabolism in liver of obese rats.[15]

There are some randomized controlled studies analyzed in a systematic review about dose-response in using turmeric or mangosteen as a supplement to control obesity.[21,22] Among those studies, there are 2 studies using 2.4 gram/day dose of turmeric or mangosteen that resulted in a reduce of body mass index (BMI), body fat percentage and total cholesterol .[23,24] When converted to rats by multiplying daily dose divide by body weight with 6.2, the dose for each rat was obtained as 270 mg/kgBW.[25] Other studies in rats also confirmed that 300 mg/kg of turmeric decreased body weight greater than 200 mg/kg; dose between 77.5-389 mg/kg of garcinia extract highly effective in suppressing fat accumulation without causing toxic effect on

testis.[26,27] Nevertheless, the exact dose for preventing retinal damage after high fat diet is yet to be confirmed.

As a drug for treating dyslipidemia, fenofibrate is a PPARα agonist that increases beta oxidation and improves mitochondrial dysfunction.[8] Several studies have shown that fenofibrate has potential role in preventing and treating neurovascular retinal diseases caused by metabolic disorders.[28,29] Nevertheless, there are some frequent side effects of fenofibrate such as gastrointestinal discomfort, musculoskeletal symptoms, skin rash, cephalgia, even rhabdomyolysis and acute renal failure.[30] Therefore, finding herbal ingredients that has a potential role in increasing PPARα in retina could be a complementary therapy for preventing and treating retinal disorder caused by HFD. This study attempted to determine the effect of turmeric and mangosteen peel extract on PPARα gene expression in the retina of HFD-induced rat model.

Methods

Sample Preparation

Upon receiving ethical approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Kristen Maranatha (No 132/KEP/IX/2022), this study was conducted. The extract of turmeric and garcinia were obtained from PT. Sidomuncul with trademark name Sari Kunyit and Sari Kulit Manggis. Each capsule of Sari Kunyit contains 500 mg of *Curcuma domesticae Rhizoma* extract, standardized 100 mg curcuminoid, equivalent to 40 g fresh turmeric; while each capsule of Sari Kulit Manggis contains 400 mg of Garcinia mangostana Pericarpium extract, equivalent to 5 g of dry ingredients.

Animals and Diet

Eight weeks Wistar rats were used in the study, with a total of 20 rats (N=4 per groups). Five groups were used in the study, consisting of negative control (-), positive control (+), *Curcuma longa* (C), *Garcinia mangostana* (G), and Fenofibrate. Negative control was a group of rats given standard chow diet, while positive control was a group of rats given high fat diet. The composition of standard chow diet was as follows: carbohydrate (48 %), protein (25 %), fat (10 %), water (10 %), cinder (6 %), calcium and NaCL (1 %); and the composition of high fat diet was as follows: carbohydrate (12.9 %), protein (16.3 %), and fat (70.8 %). Before the treatment began, the rats were adapted to the environment for two weeks. In our animal laboratory, the rats were placed in cages, one cage for each group, with the maintenance of

temperature between 18-26°C using air conditioner, relative humidity between 30-70%, and day-night cycle.

Animals' Treatment

After the adaptation process, the rats were treated as previously mentioned, the treatment included the administration of a HFD for 7 weeks, followed by HFD and the administration of turmeric extract 270mg/kg/day and mangosteen peel extract 270mg/kg/day and and Fenofibrate 15mg/kg/day for another 7 weeks. The duration of the study was conducted for 7 weeks based on the study by Adyab et al which found changes in biochemical and morphological in liver and kidney induced by high fat diet.[15]On the final day of treatments, the body weight was measured, blood was taken, then rats were terminated using ether continued by cervical dislocation, and then retina was extracted, then stored in -80°C refrigerator until further use for RNA extraction and real-time PCR.

Cholesterol and Triglyceride Measurement

The serum levels of cholesterol and triglyceride were measured using cholesterol and triglyceride assay kit (Randox Laboratories, United Kingdom) according to the manufacturer's instructions. The absorbance then measured with spectrophotometry at 500 nm for cholesterol and triglyceride (M200 Pro, USA).

RNA Extraction and Realtime PCR

RNA extraction was conducted using GENEzol reagent (GZR200, Geneaid Biotech Ltd., Taiwan), and its purity and concentration were determined by Multiskan GO (51119300, Thermo Fisher Scientific, United States). One step real-time PCR was conducted according to manufacturer's instructions using SensiFAST SYBR No-ROX One-Step Kit (BIO-72005, Bioline, United Kingdom) in AriaMx Real-Time PCR System (G8830A, Agilent, United States). Relative fold change was calculated using 2^{-ddCt}. GAPDH was used as a housekeeping gene. The primers used in the study was provided in table below.

Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY. The p-value set for the statistical difference is 0.05, and the statistical method used in the study is One-Way ANOVA/Kruskal Wallis and Tukey HSD/Mann Whitney Post Hoc Test. Normality and Homogeneity tests were conducted before applying the parametric/nonparametric test of One-Way ANOVA/Kruskal Wallis.

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Results

The difference of body weight was measured before and after the treatment, and we found a significant difference between groups with Kruskal Wallis test (P = 0.044). The difference between groups than analyzed by Post Hoc Test Mann Whitney, there were significant differences between the negative control group with the positive control group (P = 0.021), and between positive control and fenofibrate group (P = 0.043), but no significant differences found in any other groups. The result was shown in figure 1.

Table 1 Sequence Primer for PCR Analysis

Primer	Sequence	Product Size (Bp)	Annealing (°C)	Cycle	Reference
PPARα	F5'- ACGATGCTGTCCTCCTTGATG R5'- GCGTCTGACTCGGTCTTCTTG	407	59.5	35	[31]
GADPH	F5'-GTTACCAGGGCTGCCTTCTC R5'-GATGGTGATGGGTTTCCCGT	177	61	35	[32]

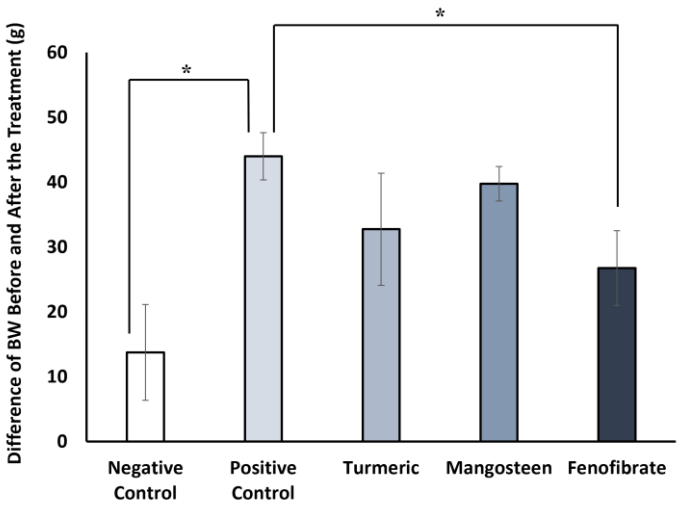

Figure 1 The Difference of Body Weight Before and After the Treatment

Description:
Negative Control: the studied animals that were given standard chow diet
Positive Control: the studied animals that were given HFD
Curcumin: the studied animals that were given HFD and turmeric extract 270 mg/kg/day
Mangosteen: the studied animals that were given HFD and mangosteen peel extract 270 mg/kg/day
Fenofibrate: the studied animals that were given HFD and fenofibrate 15 mg/kg/day
BW = body weight
* = significant ($P < 0.05$)

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Total cholesterol from the serum was measured after the treatment, and we found a significant difference between groups with Kruskal Wallis test (P = 0.009). The difference between groups than analyzed by Post Hoc Test Mann Whitney, there were significant differences between the negative control group with the positive control group (P = 0.021), between positive control and mangosteen group (P = 0.021) between positive control and fenofibrate group (P = 0.021), but no significant differences found in any other groups, although we found a tendency to decrease also in turmeric group. The result was shown in figure 2 below.

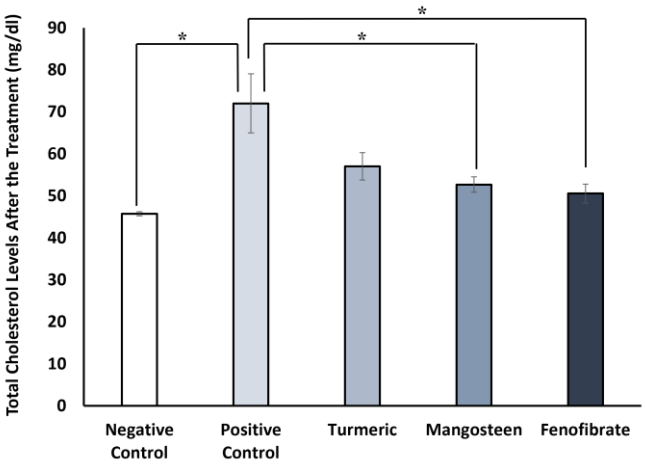

Figure 2 Total Cholesterol Levels After the Treatment

Description:
Negative Control: the studied animals that were given standard chow diet
Positive Control: the studied animals that were given HFD
Curcumin: the studied animals that were given HFD and turmeric extract 270 mg/kg/day
Mangosteen: the studied animals that were given HFD and mangosteen peel extract 270 mg/kg/day
Fenofibrate: the studied animals that were given HFD and fenofibrate 15 mg/kg/day
* = significant (P < 0.05)

Triglyceride levels from the serum were measured after the treatment, and we found a significant difference between groups with One Way ANOVA test. The difference between groups than analyzed by Post Hoc Test Tukey HSD, there were significant differences between the positive control and turmeric group (P = 0.001) and fenofibrate group (P = 0.038), but no significant differences found in any other groups. The result was shown in figure 3 below.

Research Article

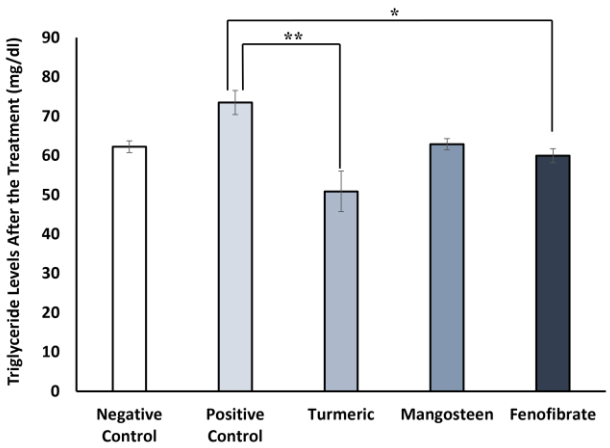

Figure 3 Triglyceride Levels After the Treatment

Description:
Negative Control: the studied animals that were given standard chow diet
Positive Control: the studied animals that were given HFD
Curcumin: the studied animals that were given HFD and turmeric extract 270 mg/kg/day
Mangosteen: the studied animals that were given HFD and mangosteen peel extract 270 mg/kg/day
Fenofibrate: the studied animals that were given HFD and fenofibrate 15 mg/kg/day
* = significant ($P < 0.05$)
** = very significant ($P < 0.01$)

The relative fold change of PPARα gene expression in the retina of HFD-induced rat model was presented in table 2. One way ANOVA test result was obtained with P=0.003, which means there are some differences of PPARα relative fold change among groups.

The difference between groups than analyzed by Post Hoc Test Tukey HSD, as shown in table 3, there were significant differences between the negative control group with the turmeric group (P = 0.009), the positive control group with the turmeric group (P=0.003).

Table 2 The Relative Fold Change and One Way Anova Test of PPARα Gene Expression in The Retina of HFD-Induced Rat Model

Variable	N	Mean ± SEM	*P*
Negative control	4	1.122 ± 0.065	
Positive control	4	0.727 ± 0.210	
Turmeric	4	3.739 ± 0.714	0.003
Mangosteen	4	2.431 ± 0.519	
Fenofibrate	4	1.774 ± 0.488	

Description:
Negative Control: the studied animals that were given standard chow diet
Positive Control: the studied animals that were given HFD
Curcumin: the studied animals that were given HFD and turmeric extract 270 mg/kg/day
Mangosteen: the studied animals that were given HFD and mangosteen peel extract 270 mg/kg/day
Fenofibrate: the studied animals that were given HFD and fenofibrate 15 mg/kg/day

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Figure 4 is the summarized result of the study. Although we found no difference in other groups, we found the tendency to increase of PPARα gene expression in mangosteen and fenofibrate groups compared to negative and positive controls; and compared to negative control, the positive control showed a lower PPARα gene expression in the retina.

Table 3 Tukey HSD Post Hoc Test of PPARα Gene Expression in The Retina of HFD-Induced Rat Model

Group	Negative control	Positive control	Turmeric	Mangosteen	Fenofibrate
Negative control		NS	**	NS	NS
Positive control			**	NS	NS
Turmeric				NS	NS
Mangosteen					NS
Fenofibrate					

Description:
Negative Control: the studied animals that were given standard chow diet
Positive Control: the studied animals that were given HFD
Curcumin: the studied animals that were given HFD and turmeric extract 270 mg/kg/day
Mangosteen: the studied animals that were given HFD and mangosteen peel extract 270 mg/kg/day
Fenofibrate: the studied animals that were given HFD and fenofibrate 15 mg/kg/day
NS = non significant
** = very significant ($P < 0.01$)

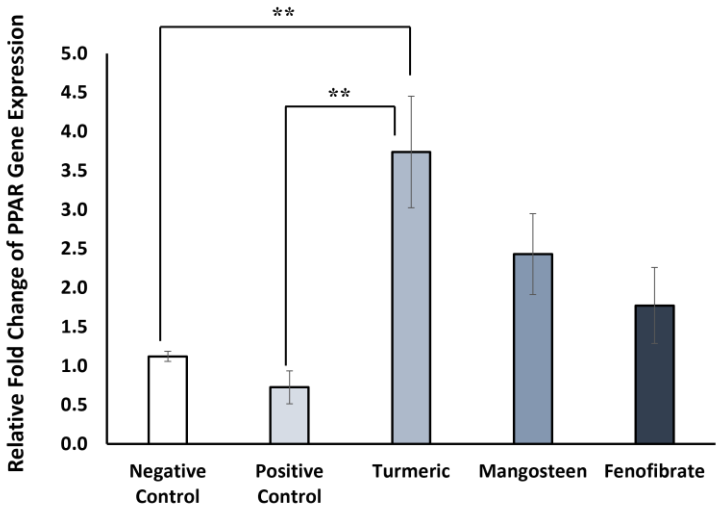

Figure 4 The Relative Fold Change of PPARα Gene Expression in The Retina of HFD-Induced Rat Model

Description:
Negative Control: the studied animals that were given standard chow diet
Positive Control: tthe studied animals that were given HFD
Curcumin: the studied animals that were given HFD and turmeric extract 270 mg/kg/day
Mangosteen: the studied animals that were given HFD and mangosteen peel extract 270 mg/kg/day
Fenofibrate: the studied animals that were given HFD and fenofibrate 15 mg/kg/day
** = very significant ($P < 0.01$)

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Discussion

High-fat diet is a risk factor for metabolic dysfunction and dyslipidemia.[1] In this study, we found an increase of body weight before and after HFD in positive control group compared to negative control group (Figure 1), accompanied with an increased level of total cholesterol (Figure 2). These result proved that HFD that were given induced an increase of body weight and total cholesterol levels, that is one of the characterization of dyslipidemia in obesity.[6] Mangosteen peel extract reduced total cholesterol levels after treatment, and this result is similar with the study conducted by Choi et al.[33] Triglyceride levels also increased in positive control group, although it was not statistically different between negative and positive control, but it differed significantly between positive control and turmeric and fenofibrate groups (Figure 3). A study by Manzoni et al showed a similar result where curcumin decreased TG and increased HDL but did not have effect on total cholesterol levels in Wistar rats model of hyperlipidemia.[34]

Dyslipidemia and metabolic dysfunction can affect retina which causes retinopathy.[8,35,36] High fat diet induce ROS production, followed by an increase in cytokine proinflammation, such as TNFα and an increase adipokines that cause chronic inflammation and oxidative stress.[37] Research shows that a high fat diet leads to downregulation of PPARα.[9] In this study, we found PPARα gene expression in positive control group is the lowest compared to all other groups. Study by Pearsall et al have shown that deficiency of PPARα in mice induced lipid transporters deficiency and retinal degeneration.[12]

Based on several studies, curcumin and mangosteen peel have anti-inflammatory effects by inhibiting NF-Kb, suppressing ROS production and increasing superoxide dismutase (SOD) activity, glutathione peroxidase (GPX) activity and glutathione (GSH) which reduce oxidative stress, inhibiting the production of proinflammatory cytokines.[14,19,20] Turmeric has more than 300 active compounds such as curcuminoid (curcumin, desmethoxycurcumin), polyphenols, sesquiterpenes, diterpenes, and triterpenoids.[38] Among all the compounds, curcumin was the main component (77%) and most studied for its activity (anti-inflammatory, anti-obesity, anti - oxidative, etc) against many diseases.[16,22,26,38,39] Curcumin was found to increase PPARα gene expression in the liver which ameliorated fatty liver disease.[40] Other study also found that γ-mangostin, metabolite compound from mangosteen activates PPARα gene expression.[41]

PPARα is a transcriptional factor that stimulates gene expression in the promoter of target genes in numerous tissue such as liver, heart, hippocampus, skeletal muscle, eyes, and kidney.[11] PPARα activation results in fatty acid catabolism and oxidation, decrease retinal vascular leakage, and reduces pro-inflammatory mediators, such as TNFα.[8,11] Dietary modulation of the lipid supply can positively influence disease with pathological

neovascularization such as diabetic retinopathy, retinopathy of prematurity, and age macular degeneration.[8,42] Oxidative stress and inflammation lead to retinal vascular damage.[42] Increasing lipid β-oxidation by transcriptional factor such as PPARα as well as dietary intervention may protect retinal function and decrease demand for neovessels.[7,42]

In this study, we found a significant difference of PPARα gene expression between the negative, positive control, and curcumin groups, as shown in Figure 4. Nevertheless, PPARα gene expression in mangosteen and fenofibrate groups also increased, although not statistically significant, compared to positive control group. Previous study has shown that curcumin reducing hepatic fat accumulation by activating AMP-activated protein kinase (AMPK) and increasing PPARα gene expression in the liver of HFD-induced mice.[39] While α-mangostin, metabolite compound of mangosteen play role on regulates liver lipid metabolism in high-fat diet induced obese mice through PPARγ pathway.[33] These differences of PPAR pathway in curcumin and mangosteen might explain the statistically significant increase of PPARα in curcumin group, and no significant increase in mangosteen group. The limitation of this study are : (1) retinal function test such as electroretinogram (ERG) or fundus photography are not demonstrated in this study, therefore we suggest to use ERG or other test to assessed retinal function ; (2) the lipid deposition in the retinal are not measured in this study; (3) the duration of HFD could be prolonged to determine the long effect of HFD on retinal lipid metabolism.

Conclusion

In conclusion, curcumin increases PPARα gene expression in the retina of HFD-induced rat model. Further research needs to investigate the specific mechanism of mangosteen and other herbal ingredients on lipid metabolism, especially in retina.

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