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EFFECTS OF WHITE TEA, GREEN TEA, AND MORINGA ON PPARγ GENE EXPRESSION IN STREPTOZOTOCIN-INDUCED RATS

Pengaruh Teh Putih, Teh Hijau, dan Moringa terhadap Ekspresi Gen PPARγ pada Tikus yang di Induksi Streptozotosin

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ABSTRACT

Peroxisome proliferator-activated receptor γ (PPARγ) has a vital role in cellular antioxidant defense systems. Several studies have reported that natural activators of the PPARγ pathway improve the development of various metabolic disorders caused by oxidative stress, including diabetes mellitus. White tea and moringa contain high amounts of antioxidants, and the flavonoid content is epigallocatechin gallate (EGCG). This study aimed to assess the effect of EGCG on PPARγ expression in the liver of diabetic experimental rats. This study used a posttest control-group design. The Sprague-Dawley male rats were assigned to several groups as follows: negative control group; diabetic (DM) group; diabetic group treated with EGCG (100 mg/kg BW) from green tea, white tea, moringa, white tea +moringa for 21 days; and baseline group (observations collected before any intervention or treatment). The diabetic condition was achieved by streptozotocin (40 mg/kg BW) induction. RNA was extracted from liver tissue, and PPARγ gene expression was further analyzed by quantitative real-time PCR. The relative expression levels of PPARγ genes were normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) using the 2-ΔΔCT formula. PPARγ gene expression in rats treated with green tea and white tea+moringa was 2.05-fold and 2.61-fold higher compared to the control group. The results of this study indicated that interventions with 100mg/kg BW EGCG from green tea and white tea + moringa upregulated PPARγ gene expression.

Keywords: moringa, PPARγ, relative expression, white tea

ABSTRAK

***Peroxisome proliferator-activated receptor γ* (PPARγ) memiliki peran penting dalam sistem pertahanan antioksidan seluler. Beberapa penelitian melaporkan efek peningkatan dari aktivator alami pada jalur PPARγ dalam perkembangan berbagai jenis gangguan metabolik yang disebabkan oleh stres oksidatif, termasuk diabetes mellitus. Teh putih dan kelor mengandung antioksidan tinggi, dengan kandungan flavonoid berupa epigallocatechin gallate (EGCG). Penelitian ini bertujuan untuk menilai efek EGCG terhadap ekspresi PPARγ di hati tikus percobaan diabetes. Penelitian ini merupakan studi eksperimental dengan desain kelompok kontrol pasca-uji. Tikus jantan Sprague-Dawley dibagi ke dalam beberapa kelompok sebagai berikut: kelompok kontrol negatif; kelompok diabetes (DM); kelompok diabetes yang diberi perlakuan EGCG (100 mg/kg BB) dari teh hijau, teh putih, kelor, serta kombinasi teh putih+kelor selama 21 hari; dan kelompok baseline (pengamatan yang dikumpulkan sebelum intervensi atau perawatan apa pun). Kondisi diabetes diinduksi dengan streptozotosin (40 mg/kg BB). RNA diekstraksi dari jaringan hati, dan pengukuran gen PPARγ dianalisis lebih lanjut menggunakan *real-time* PCR kuantitatif. Tingkat ekspresi relatif gen PPARγ dinormalisasi terhadap gliseraldehida-3-fosfat dehidrogenase (GAPDH) menggunakan rumus 2-ΔΔCT. Ekspresi gen PPARγ pada tikus yang diberi perlakuan teh hijau dan kombinasi teh putih+kelor meningkat masing-masing 2,05 kali dan 2,61 kali dibandingkan dengan kelompok kontrol. Hasil penelitian ini menunjukkan bahwa intervensi dengan EGCG 100 mg/kg BB dari teh hijau serta kombinasi teh putih+kelor meningkatkan ekspresi gen PPARγ.**

Kata kunci: kelor, PPARγ, ekspresi relatif, teh putih

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INTRODUCTION

Oxidative stress and chronic inflammation are associated with the development of metabolic disorders including diabetes. Oxidative stress is an imbalance of oxidative system in cells and tissues that will result in the overproduction of free radicals and reactive oxygen species (ROS).[1] Mammalian cells have a unique strategy in protecting themselves from the ROS-induced oxidation hazards, especially in two transcription factors; i.e., the nuclear factor erythroid 2p45-related factor 2 (Nrf2) and peroxisome proliferator-activated receptor *γ* (PPARγ) which are known to have an important role in cellular antioxidant defense systems.[2]

PPARγ can directly modulate the gene expression from antioxidant and prooxidant genes. It can also maintain the redox homeostasis through interactions between PPARγ and the signal pathways involved in oxidative stress modulation.[3] It modulates the expression of genes involved in glucose homeostasis which can upregulate the glucose transporter 4 (Glut4) and Catabolite Activator Protein (CAP) expression.[4] The disturbance in this pathway leads to the development of several diseases and pathological conditions such as obesity, obesity-induced inflammation, atherosclerosis, diabetes mellitus, metabolic syndrome, and hypertension.[5]

Researchers have reported that some antioxidant-rich plants, such as white tea (*Camellia sinensis*) and moringa (*Moringa oleifera*), exhibit antidiabetic activity.[6,7,8,9] Catechin, gallic acid, EGCG, and epicatechin form part of the flavanol or flavan-3-ol groups, which belong to the flavonoids. Tea leaves contain abundant monomers of flavanols and their derivatives.[10] The EGCG in tea acts as an anti-hyperglycemic agent by increasing insulin sensitivity, protecting pancreatic beta cells from oxidative damage, and enhancing glucose uptake in adipose tissue.[11]

Several studies have stated the activity of flavonoid as the natural activator of PPARγ. Catechin in *Camellia sinensis L. kuntze* has been identified as the natural activating product of PPARγ. It has the potential to improve the metabolic syndrome and diabetes.[4] Epigallocatechin-3-Gallate (EGCG) is a type of catechin, which is a tea polyphenol compound that has antioxidant activity. EGCG shows some activities including anti-inflammatory, anti-diabetes, anti-obesity, and anti-tumor.[12] EGCG may induce epigenetic modification by inhibiting the activity of methyltransferase and acetylase DNA in histones, leading to apoptosis.[13] The effectiveness of EGCG on PPARγ genes expression is still unspecified. Therefore, this study aimed to assess the effect of EGCG on PPARγ expression of streptozotocin-induced Sprague-Dawley rats.

METHODS

Epigallocatechin gallate (EGCG) Formula. White tea and green tea were provided by the Research Institute for Tea and Cinchona in Gambung, Indonesia. Moringa was purchased from commercially available sources. EGCG dose of 100 mg/kg BW was obtained from the extraction of each ingredient (i.e., green tea, white tea, moringa, or white tea+moringa) that was steeped in water with a temperature of 90^0C for five minutes and then filtered. The resulting filtrate was then concentrated with a rotary evaporator (temperature of 58^0C-60^0C) for 20 minutes.

The catechin analysis from the steeped tea was performed using High-Performance Liquid Chromatography (HPLC) and the standards used were catechins, gallic acid, epigallocatechin-3-gallate (EGCG), and epicatechin (EC). The standard used had high purity level at 98 percent and 80 percent for gallic acid and EGCG respectively. Meanwhile, the catechin standard used in this study was obtained from Sigma Aldrich. The standard solution (1 mg/ml) was prepared by adding 0.05 percent formic acid in 70 percent acetonitrile to the standards. The HPLC system consisted of Smart Line HPLC Knauer GmBH with a UV detector (Smart Line UV Detector 2500 A 5140)®, Smart Line Dual Pump 1000 V 7603, and Rheodyne Loop A135 sample injector with a 20 µl volume. The column used was Eurosphere C-18 (250×4.6 mm ID, 5µm). The reverse phase HPLC in this study used an isocratic mobile phase elution system which was a mixture of 0.1 percent orthophosphoric acid, water, acetonitrile, and methanol (14:7:3:1 v/v/v/v) at a pH value of

4 and a flow rate of 1.2 ml/min. Detection was performed at a wavelength of 280 nm.[14]

Animal Study. This animal study had been approved by the Animal Ethics Committee of IPB University, Bogor, Indonesia (Number 66-2017). A total of 28 Sprague-Dawley male rats (12-week old, 200-300 g) were used for this study. The rats were obtained from Indoanimal Laboratory in Bogor, Indonesia. All rats were acclimatized to the new environmental conditions for two weeks before the experiment began. They were housed under standard laboratory conditions of 12-12-h light-dark cycle, and they were fed with standard diet and ad libitum water. The rats were randomly divided into seven groups as follows: (i) positive control group (DM); DM groups receiving EGCG (100 mg/kg BW) from (ii) green tea (GT), (iii) white tea (WT), (iv) moringa (K), (v) white tea+moringa (WTK); (vi) normal group (N); and (vii) baseline group. The intervention was conducted for 21 days. A total of 2 g of each ingredient (white tea, green tea, kelor, and a mixture of white tea and kelor with 1:1 ratio) was steeped in 100 ml of water at 90 0C for five minutes and then filtered using filter paper. The intervention groups were given the steeped tea or kelor using feeding tubes with an EGCG dose of 100 mg/kg BW. The oral gavage was carried out at 9-10 a.m. All groups received standard feed and ad-libitum drinking. With an EGCG dose of 100 mg/kg BW, the total ingredients required were 2.2 g white tea, 7.75 g green tea, 4.13 g kelor, and 4.06 of the white tea and kelor mixture. The steeped tea or kelor sample was concentrated using a rotary evaporator at a temperature of 58-60 0C for 20 minutes so that the tea or kelor could be administered orally to the rats.[15] The diabetic condition (blood sugar level of >126 mg/dl), except for N group, was achieved by streptozotocin induction in a dose of 40 mg/kg BW. After 21 days of intervention, the rats were euthanized, and their livers were removed.

Primer Design. The specific primer sequences for PPARγ and GAPDH encoding genes were designed using Mega 6.0 and BioEdit (Table 1). The mRNA sequence encoding the *Rattus norvegicus* fragment of the PPARγ gene was used as a template to design the primer. The housekeeping gene (GAPDH) was used as the reference gene, and the mRNA sequence which encoded *Rattus norvegicus* GAPDH gene was used to design the primer. The full sequences of the PPARγ and GAPDH genes were taken from the GenBank database (http://www.ncbi.nlm.nih.gov).

RNA Extraction. Liver tissues were immersed into RNA later solution (Qiagen, US) for 24 hours and kept in -80^{0}C. The rat's total mRNA was extracted from 30-50 mg of liver tissue using the RNeasy Mini Kit (Qiagen, US) according to the manufacturer's instructions. The quality and quantity of RNA were further evaluated by measuring A260/230 and A260/280 values using NanoDrop 2000 (Thermo Fisher Scientific, USA). The cDNA was synthesized from 1 µg of total RNA using ReverTraAce qPCR RT Master Mix with gDNA Remover Kit Toyobo (Japan).

Table 1
Primer sequences used for qRT-PCR

Gene	Accession number	Primers	Length
PPARγ	NM_001145366.1	F : 5'-CCATCCGCATTTTTCAAGGG-3'	134 bp
		R : 5'-GACACCATACTTGAGCAGAG-3'	
GAPDH	NM_017008.4	F : 5'-CAGAACATCATCCCTGCATC-3'	157 bp
		R : 5'-CATACTTGGCAGGTTTCTCC-3'	

Assessment of mRNA Gene Expression. Quantitative real-time polymerase chain reactions (qRT-PCR) were performed in the Analytik Jena qTOWER using THUNDERBIRD Sybr qPCR Mix Toyobo (Japan). The master mix for qRT-PCR consisted of 5 µl of THUNDERBIRD Sybr qPCR Mix Toyobo, 1 µl cDNA (60 ng/µl), 0.5 µl (25 pmol) of the forward and reverse primers, 3 µl nuclease-free water, in a total volume of 10 µl. All incubation included initial denaturation at 95^0C for 1 min, and 40 cycles of denaturation (15 sec at 95^0C) and annealing (1 min at 60^0C) subsequently. The housekeeping gene (GAPDH) was used as the reference gene. Gene expression levels were calculated based on the cycle threshold (Ct) value using the following formula:

ΔCt (intervention) = Ct (intervention) – Ct (GAPDH)
ΔCt (control) = Ct (control) – Ct (GAPDH)
$\Delta\Delta Ct = \Delta Ct$ (intervention) – ΔCt (control)
Respective gene expression level = $2^{-\Delta\Delta CT}$

Statistical analysis. The results were expressed as mean±SD $2^{-\Delta\Delta CT}$. The statistical analysis was performed by using one-way Analysis of Variance (ANOVA) followed by Duncan's post hoc test using SPSS (version 23). The value of $p<0.05$ was considered statistically significant.

RESULTS

PPARγ gene expression results as shown in Table 2 indicated that mRNA expression of PPARγ as a result of transcription process on rats after the intervention using green tea (EGCG 1.29%[16]) and white tea+moringa were 2.05-fold and 2.61-fold higher than the control group, respectively. The PPARγ gene expressions after white tea and moringa (EGCG 2.42%[16]) interventions were 0.70-fold and 0.43-fold lower than the control group, respectively. PPARγ gene expression in normal rats was 3.39-fold higher, while the PPARγ gene expression in the baseline group was 0.06-fold lower. The results are presented in the bar chart in Figure 1.

The results of the study before blood glucose measurement on day 0 (the first day of hyperglycemia) showed a significant difference in blood glucose in the normal group compared to the STZ-induced group ($P<0.05$). The average blood glucose of STZ-induced mice reached 390.53 + 83.9, while in the normal group it was only 69.75 + 13.47 mg/dl. Based on the paired t-test between blood glucose measurements on H-0 and H-21, the KN, WT, and K groups did not show significant changes in fasting blood glucose ($p>0.05$), while the group given green tea (GT) and a mixture of white tea + moringa tea (WTK) experienced a significant decrease in fasting blood glucose ($p<0.05$).[16]

Table 2
PPARγ Gene Expression at The Level of Transcription (-fold)

Group	PPARγ gene expression (-fold)	*p-value*
DM	1^{ab}	0.004*
GT	2.05^{bc}	
WT	0.70^{ab}	
K	0.43^{a}	
WTK	2.61^{c}	
Normal	3.39^{c}	
Baseline	0.06^{a}	

PPARγ: Peroxisome proliferator-activated receptor γ ; CAP : Catabolite Activator Protein ; EGCG ; epigallocatechin gallate ; GAPDH : glyceraldehyde-3-phosphate ; dehydrogenase ; ROS : reactive oxygen species ; Nrf2 : nuclear factor erythroid 2p45-related factor 2 ; Glut4 : glucose transporter 4 ; DM Group : Diabetes Melitus Group ; GT : Green Tea ; WT : White Tea ; K : Kelor (Moringga) ; WTK ; white tea+moringa ; N ; Normal group ; Ct ; cycle threshold ; DNMT : DNA methyltransferase
*ANOVA followed by Duncan's *Post Hoc Test,* significant at $p<0.05$. The alphabetical notifications showed significant differences.

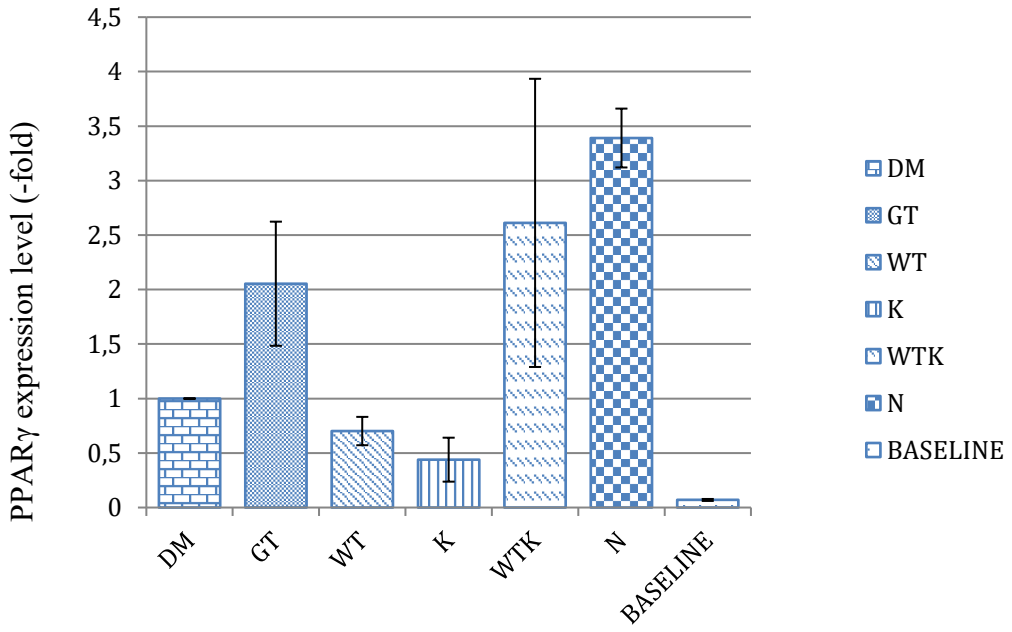

Figure 1
The Comparison of PPARγ Gene Expression at the Level of Transcription between the Intervention Groups (GT, WT, K, and WTK), Normal Group (N), Baseline Group, and Control Group (DM)

DISCUSSION

Animal studies using green tea have shown the potential of tea's active compounds as antihyperglycemic agents. Administering green tea containing 100 mg/kgBW to alloxan-induced Wistar rats for four weeks reduced blood glucose by 57.9 percent.[17] EGCG in green tea can also increase insulin sensitivity, protect pancreatic beta cells from oxidation, and increase glucose uptake in adipose tissue. Green tea infusion can suppress the activity of the α-glucosidase enzyme by 86.7 percent.[18]

In addition to green tea, White tea is one of the types of tea obtained from the tea shoots in the form of buds. It does not go through fermentation; thus, its catechin content is higher than green tea.[19] White tea has antihyperglycemic activity and can reduce serum total cholesterol and LDL levels.[7,19] It can also limit free radicals by binding them to reactive oxygen species (ROS).[6,20]

Moringa (*Moringa oleifera*), a native plant from India, grows in tropical and subtropical regions. It is also known as a drumstick or horseradish tree. Its leaves contain abundant minerals, vitamins, and other essential phytochemicals. Researchers have reported that moringa (kelor) has antidiabetic properties,[21,22,23,24] antihyperglycemic, and antihypertriglyceridemic activities.[25,26] Ambarwati[27] demonstrated that administering *Moringa oleifera* extract at a dose of 500 mg/kg body weight for 21 days significantly ameliorated blood glucose levels in streptozotocin-induced diabetic rats. Likewise, Malki and Rabey [22] reported that treatment with *Moringa oleifera* at doses of 50 and 100 mg/kg body weight for four weeks markedly improved the pancreatic histopathological architecture in streptozotocin-induced diabetic rats.

A study by Amalia[16], found that the administration of white tea (WT) or moringa (K)

alone for 21 days has not been able to reduce blood glucose significantly, while the group given white tea + moringa tea (WTK) with a ratio of 50 percent: 50 percent was able to reduce fasting blood glucose significantly. The decrease in blood glucose in the WTK group was substantially different from the Negatif control (KN) group but not significantly different from the GT group. The WT and K groups also experienced significant weight loss, while the WTK group was able to prevent significant weight loss. The weight loss in the WTK group was significantly different from the KN group but not significantly different from the green tea (GT) group.

The selection of GAPDH as an internal gene in this study was based on several previous studies. The housekeeping gene has been commonly used as an internal control for normalizing gene expression. It is commonly expressed in all cells of the organism at all the same levels since it is assumed that the gene is needed for the basic function of cell maintenance as a constitutive gene.[28] The most appropriate selection of housekeeping genes is important for the study of mRNA gene expression, especially in hyperglycemia cases, because it may affect the housekeeping gene expression.[29] Glyceraldehyde-3-Phosphate dehydrogenase (GAPDH) has been mostly used as a housekeeping gene. GAPDH is an enzyme that catalyzes the sixth stage of the glycolysis process, a process that converts glucose into pyruvate. It also has a role in DNA repair and transcriptional regulation.[30] A previous study found that GAPDH was the most stable housekeeping gene in gene expression analysis in the rat models of acute pancreatitis.[31]

Streptozotocin induction causes cell cytotoxicity due to DNA methylation through the formation of carbonium ions, leading to the activation of nuclear enzyme ADP-ribose synthetase. It causes the NAD^+ reduction. Other pathways associated with cell death are nitric oxide production, free radical generation as hydrogen peroxide, and the changes in NF-κB signal transduction pathway.[32] The induction of streptozocin had 0.06-fold lower effect on PPARγ gene expression in the baseline group compared to the normal rats (3.39-fold higher). This result was in line with a previous study that found that the streptozotocin induction caused a decrease in PPARγ expression levels up to 80 percent.[33]

The intervention using EGCG from green tea upregulated the PPARγ gene expression (2.05-fold higher). In this study, green tea intervention was proven to modulate the PPARγ gene expression. This result was in line with the previous study.[4,34,35] The intervention using white tea caused a level of PPARγ gene expression that was 0.70 fold; this result was in contrast to the previous study, suggesting that white tea could upregulate the PPARγ gene expression in lung cancer cell lines. The upregulation of gene expression was higher than that of the green tea intervention.[36]

The intervention using moringa caused the down-regulation of PPARγ gene expression (0.43-fold lower). It was probably due to the quercetin content in moringa. Moringa leaves are rich in quercetin (100 mg/100 g).[37] Quercetin content of green tea was between 0.21 mg/100 g and 2.77 mg/100 g.[38] The quercetin content of white tea was not identified. This result was similar with the previous studies which reported that quercetin downregulated the PPAR-γ.[39,40,41]

The intervention using a combination of white tea and moringa showed different results compared to “moringa only” and “white tea only” interventions. The mixture of moringa and white tea resulted in an upregulation of PPARγ gene expression (2.61-fold higher), and this result was not significantly different from the PPARγ gene expression in normal rats (3.39-fold higher). This result suggested that synergistic flavonoid from white tea and moringa might cause an increase in PPARγ gene expression. The quercetin content of moringa might affect the flavonoid content of white tea. This result was supported by the previous study indicating that quercetin might also influence the bioavailability of some dietary supplements. The quercetin seems to improve the bioavailability of EGCG[42] and possibly other flavonoids.[43]

Flavonoids possess many biochemical properties; the best described is their capacity to act as an antioxidant.[10,44,45] The antioxidant mechanisms may include: (1) the suppression of ROS formation either by inhibition of enzymes or by chelating trace elements involved in the free radical generation; (2) scavenging ROS; and (3) upregulation or protection of antioxidant defences.[39] Catechin significantly induces PPARγ transcriptional activation at a certain dosage. A dosage of 10 μM catechin produces double PPARγ transcriptional activity. The lower

concentrations of these molecules do not affect PPARγ transcriptional activation.[46] Gene expression is related to the DNA methylation mechanism. PPARγ expression has been reported to be repressed by DNA methylation in diabetic model rats. [47] Some recent studies have shown that bioactive food components, including essential and non-essential nutrients, can modify the DNA methylation patterns in a complex way.[48] Several studies have described that catechins and EGCG modulate DNA methylation by attenuating the effects of DNMT1, but the mechanism is still unknown. It may involve the direct inhibition of enzymes and the reduced expression and translation of DNMTs.[49,50,51] EGCG concentrations (<1 μM) can directly inhibit DNA methyltransferase (DNMT) by binding to DNMT.[51]

The combination of white tea and *Moringa oleifera* may exert a synergistic effect. This synergistic interaction could influence multiple biochemical pathways by affecting the activities of various enzymes, substrates, metabolites, receptors, ion channels, transport proteins, and ribosomal DNA/RNA. Furthermore, physicochemical and pharmacokinetic interactions between white tea and *Moringa oleifera* may enhance the solubility and bioavailability of the combined extracts.[52] Further studies are required to evaluate different ratios of white tea and *Moringa oleifera* extracts to obtain more comprehensive data on their effects on lipid profiles.

The results of several studies above that were associated with the results of this study indicated that the same EGCG dose from different types of tea produced different PPARγ gene expression. The presence of flavonoid content may cause the upregulation of the PPARγ gene expression mechanism. The synergism of the flavonoids in the antioxidant defence system also occurred because the flavonoids cause the attenuation of DNA methylation, which will then lead to the upregulation of PPARγ gene expression in diabetic model rats. These results were seen in the green tea and a combination of white tea and moringa interventions. The downregulation of PPARγ gene expression in the moringa group might be due to the higher quercetin content in moringa than in green tea and white tea. The downregulation of PPARγ gene expression in the white tea group might be caused by different dosages and the type of study conducted, thereby producing differences.

CONCLUSION

The plant-based interventions such as green tea, white tea, and Moringa oleifera modulate PPARγ gene expression in diabetic rats through their flavonoid and antioxidant activities. As result, the combination of white tea and Moringa oleifera produced a synergistic effect, restoring PPARγ expression to near-normal levels.

RECOMMENDATION

The intervention using EGCG of 100 mg/kg BW from white tea + Moringa upregulated the PPARγ expression of streptozocin-induced Sprague-Dawley rats.

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