Trop J Nat Prod Res, September 2025; 9(9): 4517 - 4523 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Decaffeinated Green Tea and Green Coffee Extract Attenuate Cardiac Perivascular Fibrosis in a Metabolic Syndrome Model by Decreasing Fibroblast Growth Factor 23 and Runt-related transcription factor 2 Expression

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ARTICLE INFO

Article history:
Received 08 June 2025
Revised 26 August 2025
Accepted 27 August 2025
Published online 01 October 2025

ABSTRACT

Metabolic syndrome includes hypertension, obesity, and insulin resistance, which increase the risk of cardiovascular disease (CVD) by up to 50%. This condition activates genes, such as FGF23, GALNT3, and RUNX2, causing heart fibrosis. This study aimed to determine the effect of tea and coffee extract therapy on perivascular fibrosis in the heart of a mouse model of metabolic syndrome and its impact on the expression of fibrosis-related genes such as FGF23, GALNT3, and RUNX2. This study used 25 male Sprague Dawley rats, divided into five groups (n=5): negative control (NORM), positive control (METS), metformin therapy (MFN), green tea and green coffee extract therapy (GTCE), and a combination of both (COMB). The METS samples were fed a high-fat and high-sucrose diet for 18 weeks, followed by a low-dose Streptozotocin injection (30 mf/kgBW) for 11 weeks. The METS model was then administered treatment for 9 weeks. After treatment, the rats were dissected, and the heart organs were analyzed with Masson Trichrome, and FGF23, GALNT3, and RUNX2 mRNA expression was measured by RT-PCR. The results showed that green tea and coffee extracts, alone or in combination with metformin, showed anti-fibrotic effects by reducing collagen deposition (5.87% ± 0.66 and 4.14% ± 0.66) and lowering FGF23 (0.543 ± 0.112 and 0.676 ± 0.159) and RUNX2 (2.716 ± 0.482 and 7.325 ± 0.899). These results suggest that combination extracts exhibit anti-fibrotic effects by reducing collagen deposition in perivascular area. They also suppress pro-fibrotic genes, such as FGF23 and RUNX2, which are involved in cardiac fibrosis.

Keywords: FGF23, Heart Fibrosis, Green Tea, Green Coffee, Metabolic Syndrome

Introduction

Metabolic syndrome (METS) is a clinical condition that consists of several pathological conditions, such as obesity, hyperglycemia, hypertension, insulin resistance, dyslipidemia, and atherogenicity.[1,2] Factors such as sex contribute to its prevalence, with metabolic syndrome being more common in men. However, hormonal dysregulation after menopause increases this risk in women [3,4]. The global prevalence of METS ranges from 12% to 31%, with the highest rates in the American and Eastern Mediterranean racial groups. The prevalence of obesity increased by 82% from 1990 to 2010, reflecting a global rise in obesity. [5,6] Metabolic syndrome is linked to the progression of cardiovascular disease. A person suffering from METS is known to have a potential risk of suffering from cardiovascular disease (CVD) 50-60% higher than those without the syndrome.[7] Individuals with metabolic syndrome and CKD often have calcium and phosphate imbalances, leading to their buildup in the blood and resulting in vascular calcification.[8,9]

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Citation: Rahmad Darmawan, Ira Humairah, Ema Qunianingsih, Ervi A. Munthe, Linda. Effect of *Annona muricata* L. (Soursop) on Blood Glucose Level in a Diabetic Rat Model: A Meta-Analysis. Trop J Nat Prod Res. 2025; 9(9): 4517 – 4523 https://doi.org/10.26538/tjnpr/v9i9.53

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Individuals with metabolic syndrome and mineral metabolism disorders are at high risk for Left Ventricular Hypertrophy (LVH), where the left ventricle thickens and increases in mass [10]. Studies have shown that interstitial and perivascular fibrosis may be present in the hearts with LVH.[11] Mineral abnormalities lead to increased expression of calcification-related genes such as Fibroblast Growth Factor 23 (FGF23) and runt-related transcription factor 2 (RUNX2). [12,13] Elevated FGF23 concentrations in the blood can cause left ventricular hypertrophy (LVH) by thickening the walls of the heart ventricles and increasing serum Angiotensin II levels.[14] Angiotensin II binds to its receptor (AT1R) on cardiomyocytes, promoting hypertrophy and fibrosis in the heart.[15] FGF23 activity is also regulated by polypeptide N-acetylgalactosaminyltransferase-3 (GALNT3), which facilitates the O-glycosylation of FGF23 at amino acid Thr178, preventing its cleavage and enabling it to exert hormonal effects. Additionally, when overexpressed, RUNX2, a transcription factor in mineral metabolism, can lead to aortic stiffness and medial fibrosis in vascular smooth muscle cells (VSMC), mediating pro-fibrotic responses in human aortic smooth muscle cells.[16] Metformin was designed as an anti-diabetic agent in 1950 and was then used in several other diseases because it showed beneficial therapeutic effects and minimal side effects.[17] Metformin improved fibrosis by interfering with the TGF-β signaling pathway and cell metabolism and suppressing oxidative stress.[18,19] The anti-fibrosis effect of metformin was seen to reduce extracellular matrix (ECM) remodeling abnormalities in visceral fat of obese rat models and subcutaneous adipose tissue in rats being treated with doxorubicin. [20,21] Tea and coffee are the most widely consumed beverages worldwide, and they are known for their bioactive compounds that benefit the cardiovascular system. They are rich in polyphenols, such as catechins (EGCG, EGC, and ECG), and are abundant in tea and coffee. Additionally, chlorogenic acid (CGA) in green coffee is recognized for

its potent antioxidant potential.[22] The previous research has used a combination of decaffeinated green tea and green coffee extracts (GTCE) to investigate its effect on the condition of metabolic syndrome rat models. The previous study showed that tea and coffee work synergistically and improve metabolic parameters that worsen due to metabolic syndrome, such as increased high-density lipoprotein (HDL) in the blood.[23] Other studies using green tea extract as monotherapy for metabolic syndrome are known to improve hyperglycemia via modulation of IRS-1 and GLUT4.[24] Furthermore, another study of this combination also successfully reduced serum angiotensin II levels and the level of inflammatory genes related to fibrosis, such as IL-6, Tgf-*β*1, NF-κB, TNF-α, Rac-1, and α-SMA.[25]

Therefore, using GTCE for treatment is rarely performed, especially for tea and coffee, which require decaffeination. This aimed to evaluate the effects of administering GTCE as an additional therapeutic agent with metformin in treating perivascular fibrosis in the heart organs of a metabolic syndrome rats model by decreasing the expression of genes responsible for the mineral metabolism processes such as FGF23 and RUNX2.

Materials and Methods

Research Design

This study employed an experimental with a post-test control group setup and a simple random sampling technique. This approach was selected to test and determine the effects of a treatment or intervention—Male Sprague Dawley rats, 150 g and aged 4 weeks, acclimatized for 7 days. After acclimatization, the rats were divided into five groups (n = 5): a negative control group (NORM) and a positive control group (METS). The rats in the METS group were fed a high-fat, high-sugar diet to model metabolic syndrome. In the 10th to 11th week, rats were injected with 30 mg/kg BW of Streptozotocin (STZ) dissolved in 10% citrate buffer pH 4.5, with an average body weight of 480-500 grams. Rats that met the METS criteria defined by NCEP ATP-III were selected. These criteria include fasting blood glucose levels >200 mg/dL, HDL <40 mg/dL, and triglyceride levels >200 mg/dL for approximately 4-6 weeks. Rats successfully induced with METS were then divided into treatment groups: metformin therapy (MFN) 100 mg/kg BW, decaffeinated tea and coffee extract therapy (GTCE) 200 mg/kg BW and 300 mg/kg BW; and a combination therapy group (COMB) 100, 200, and 300 mg/kg BW, respectively. The doses were based on previous studies that have shown promising results and are safe to administer.[25] The therapeutic materials were dissolved in water and administered using a syringe for 9 weeks.

Plant Material

The green tea leaves were young leaf shoots from a tea plantation in Ciwidey (7°9'24.48' 'S, 108°0'23.4' 'E), Indonesia. The green coffee used was premium robusta beans sourced from Dampit (8°44'16.64"S, 113°41'52.26"E), Indonesia. Reference number TSN-506801 for green tea and KAD-001 for green coffee beans were used. Samples of tea leaves and coffee beans were collected in September 2024. After sorting to remove contaminants and low-quality samples, the plant materials were stored at the the appropriate temperature in a dry, dark environment to preserve their quality.

Experimental Animal

The animal model design for metabolic syndrome followed previous research procedures.[22] The male Sprague-Dawley rats in this study were 8-week-old rats with an average weight of 250-300 grams obtained from BPPOM Jakarta. The research process began with a 7-day acclimatization period. The rats were provided food and drinks according to laboratory standards during acclimatization. Water was provided *ad libitum* using the drip method to avoid contamination of rat feces. To achieve metabolic syndrome, all rats except the negative control group will be given a special high-fat and high Sucrose (HFHS) diet. The diet consisted of standard pellets, egg yolk, sucrose powder, hydrogenated vegetable fat, salt, methionine, and monosodium glutamate. Standard rat pellet feed was converted into powder form by grinding, adding 15% egg yolk, 20% fat, 20% sucrose, 2% MSG, and 0.5% methionine. After acclimatization, all rats, except those in the control group, were fed a high-fat, high-sugar (HFHS) diet for 18 weeks. At week 12, the rats received a streptozotocin (STZ) injection to enhance the development of metabolic syndrome. By week 18, the rats' biochemical parameters, including blood glucose levels, HDL, and triglycerides, must meet the NCEP ATP-III criteria and remain stable for 6 weeks.

Ethical clearance

The experimental design was approved by the Health Research Ethics Committee of the Faculty of Medicine at Universitas Brawijaya, Malang, Indonesia, under the registered number 34/EC/KEPK-S2/01/2024.

Green Tea and Decaffeinated Green Coffee Extraction

Green coffee beans roasted at 180°-200°C for 6-8 hours until the first crack, achieving an 8-10% water content. The beans were ground, macerated with 95% ethanol, and filtered to split the liquid and solid phases. The liquid was put into the rotary evaporator at ± 40°C. Both extracts are partitioned with water and analyzed by column chromatography with silica gel as the static phase, followed by evaporation of the filtered product.

Histological Analysis

The heart organ was separated and prepared using paraffin blocks. The samples were then sliced to a 3-8 µm thickness and placed on a glass object. The samples were then stained using Masson's Trichrome kit. The samples were then observed under a light microscope (Nikon Eclipse LV100D-U 300 megapixels, Nikon Corporation Industrial Metrology, United States) and photographed. The results of the observations were then analyzed using ImageJ software to quantify collagen deposition in the heart samples.

Measurement of FGF23, GALNT3, and RUNX2 Gene Expression

Gene expression measurement began with RNA extraction from the heart organ using the PrimeZol reagent. Approximately 3 g of heart tissue was prepared in a sterile mortar and crushed with a pestle until partially crushed. Next, 500 µL of PrimeZol was added, and the tissue was homogenized until it became smooth. Reverse Transcription was performed using a Thermo Fischer Scientific kit. RNA expression was analyzed using the Light Cycler 96 (Takara, Japan). The enzyme used for PCR was the GoTaq Green Master (Promega, USA), following the manufacturer's procedure. The primer sequences used are listed in Table 1. The PCR cycle consisted of 30 cycles with the following settings: 5 min at 95°C for pre-denaturation (one cycle), denaturation at 95°C for 31 s, annealing at 55.3°C (*β*-actin), 58.3°C (FGF23), 60°C (GALNT3), and 55.3°C (RUNX2) for 30 s, extension at 72°C for 30 s, and extension at 72°C for 10 min. The expression of the genes was normalized to *β*-actin expression. The results are analyzed using ImageJ software and replicated thrice for each sample.

Table 1: List of primer

β-actin	Forward: 5'- TGA GAG GGA AAT CGT GCG TGA CAT-3' Reverse: 5'-ACC GCT CAT TGC CGA TAG TGA TGA-3'
FGF23	Forward 5'-CGT CTC TTG CCT AGC GTT CT-3' Reverse 5'-ACT CTG TGG AGT GGG CTT TG-3'
GALNT3	Forward: 5'- CTA CAC CGC AGC AGA GTT GA-3' Reverse: 5'- TCG CAA AGG CGT TGA AAC AG-3'
RUNX2	Forward: 5'- CAG TTC CTA ACG GGC ACC AT-3'' Reverse: 5'- TTA GGG TCT CGG AGG GAA GG-3'

Statistical Analysis

The FGF23, GALNT3, and RUNX2 mRNA expression data in each group were presented as mean values. Histological data on collagen deposition were expressed as a percentage of cardiomyocyte tissue area across five fields of view and averaged for each sample. Normality test

and homogeneity were assessed using the Kolmogorov-Smirnov and Levene tests, respectively. ANOVA was used for statistical data analysis, complemented by Post Hoc Duncan tests using IBM SPSS software version 25.

Results and Discussion

Histological Analysis of Heart Organ

Masson's Trichrome staining revealed excessive collagen deposition in the perivascular area under METS conditions, indicating perivascular fibrosis (Figure 1A). The NORM group showed significantly less collagen than the METS group did. Therapy groups exhibited reduced collagen deposition: the metformin therapy group (MFN) averaged 7.15% ± 1.05, the decaffeinated green tea and coffee extract group (GTCE) averaged 5.87% ± 0.66, and the combination therapy group (COMB) had the lowest value at 4.14% ± 0.66. In contrast, the METS group averaged 11.68% ± 1.44, whereas the NORM group averaged 4.98% ± 1.02. Statistical analysis confirmed significant differences between the therapy and METS groups (Figure 1B).

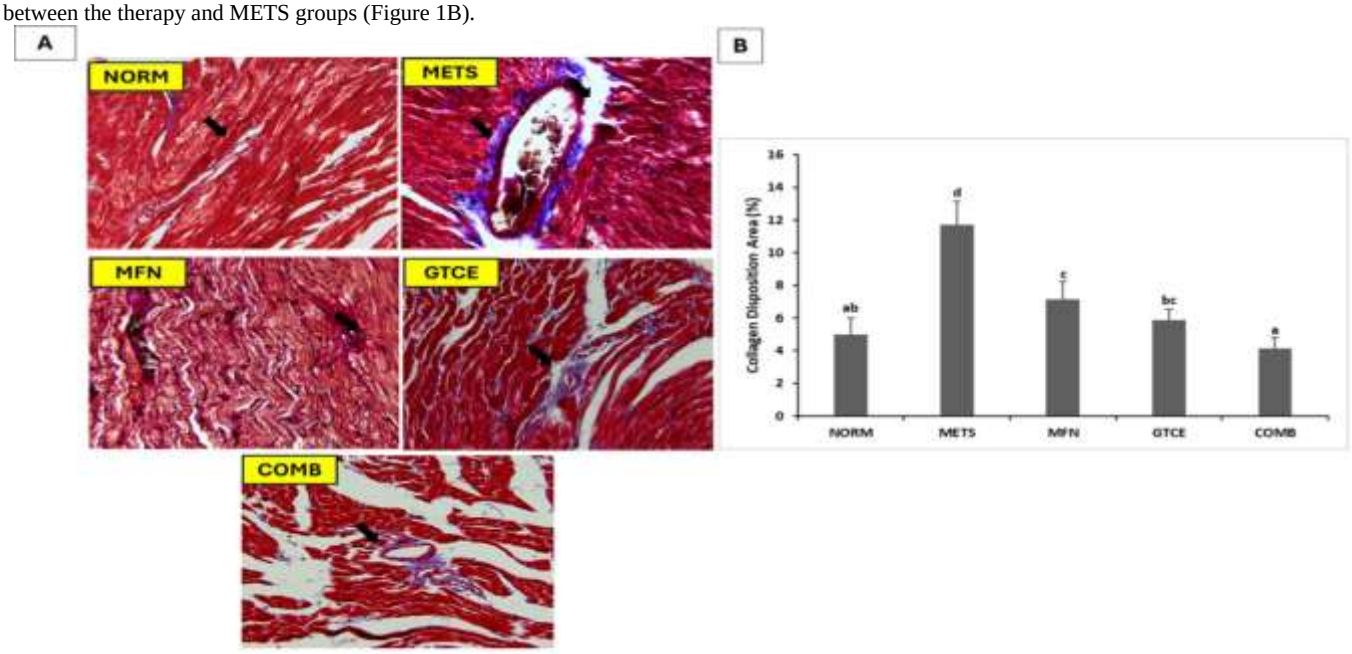

Figure 1: Comparison of histological structures in myocardial tissue. A) Histological cross-section of myocardial tissue, and B) Results of analysis of the extent of collagen deposition formed. Different subset signs in each group indicate significance p<0.05. Arrows indicate perivascular fibrotic lesions marked in blue: Masson's Trichrome staining, 200x magnification, Nikon Eclipse LV100D-U 300 megapixels. Different notations indicate significant differences (p<0.05).

Measurement of FGF23 mRNA Expression

The densitometry results showed an increased relative expression of FGF23 (FGF23/β-actin) in the METS group, averaging 1.847 ± 0.179, compared to the NORM group with an average of 0.588 ± 0.148 (Figure 2A). In the therapy group, FGF23 expression approached normal levels: MFN averaged 0.739 ± 0.155, GTCE averaged 0.543 ± 0.112, and COMB averaged 0.676 ± 0.159. Statistic analysis confirmed that the therapy reduced FGF23 expression to near-normal levels with significant differences (p<0.05) between the METS group and all the other groups. FGF23 has been shown to cause various cardiovascular problems, such as Left Ventricular Hypertrophy (LVH), which leads to cardiac fibrosis. FGF23 induces LVH by activating FGFR4, which then triggers the calcineurin signaling pathway, ultimately contributing to perivascular fibrosis. [30] Based on Figure 2B, this study showed that FGF23 expression was significantly increased in the METS group. Administration of MFN or GTCE resulted in a decrease in FGF23 expression. The increased FGF23 expression in METS conditions may be influenced by obesity caused by a high-fat sucrose diet, which can trigger dyslipidemia and insulin resistance. The decrease in FGF23 expression after MFN or GTCE administration may be due to its ability to repair various metabolic and inflammatory pathways. Metformin effectively reduces FGF23 expression by increasing insulin sensitivity by activating the PI3K/PKB/Akt pathway and activating the transcription factor forkhead box protein O1 (FOXO1).[31] Another research showed that 100 mg/kg of green tea extract can reduce FGF23, improving kidney function and renal fibrosis.[32]

Measurement of GALNT3 mRNA Expression

Densitometry analysis using ImageJ software showed similar GALNT3 (GALNT3/β-actin) expression in the NORM and METS groups (Figure 3A). The METS group had an average score of 0.593 ± 0.171, while that of the NORM group was 0.719 ± 0.134. The MFN group had an average level of 0.711 ± 0.235 in the therapy group. The GTCE group showed a significant increase in expression, with an average of 1.384 ± 0.458, while the COMB group had a similar expression to GTCE, with an average of 0.971 ± 0.286. One-way ANOVA followed by Duncan's post-hoc test revealed that the GTCE group had significantly higher GALNT3 expression than the other groups (Figure 3B). One of the groups of enzymes from the GalNAc-Ts family, Polypeptide N-acetyl-galactoacyl-transferase 3 (GALNT3), functions to initiate mucin-type O-glycosylation of the side chains of Serine/Threonine residues of proteins. [33] GALNT3 works by influencing the expression of FGF23, which is known to be responsible for the O-glycosylation of FGF23 by providing mucin type-O glycan on the Thr178 residue, which then causes FGF23 to avoid the cleavage process so that FGF23 is present in an intact condition.[34] The presence of intact FGF23 is also often

Metabolic syndrome, induced by HFHS consumption, significantly contributes to cardiovascular disorders, such as cardiac hypertrophy and fibrosis.[26] Cardiac fibrosis can be divided into cardiac interstitial fibrosis, characterized by the extracellular matrix or collagen tissue build-up in the endomysial and perimysial spaces. In contrast, cardiac perivascular fibrosis refers to the accumulation of extracellular matrix around blood vessels.[27,28] This study found an increase in collagen tissue that was successfully identified as a blue color in histological preparations stained using the Masson's Trichrome method (Figure. 1A). This study also observed an increase in collagen tissue identified as blue in histological preparations stained with the Masson's Trichrome method (Figure 1B). This could be due to damage to the endothelial area around the perivascular region, which stimulates the wound-healing mechanism. Previous research supports this finding, explaining that a high-fat diet increases salt intake, which causes hypertension. This, in turn, leads to ventricular hypertrophy, increased arterial pressure, and potential endothelial damage, all of which can trigger cardiac fibrosis.[29]

observed in patients with metabolic syndrome, so this is thought to be the leading cause of the development of fibrosis in patients with metabolic syndrome.[31] Based on its activity, GALNT3 is considered an upstream regulator of FGF23.[35] Based on Figure 3B, this study observed increased GALNT3 expression in GTCE and COMB therapies. These results suggest that GALNT3 may have other functions influenced by GTCE and COMB treatment, which are not yet fully understood and warrant further investigation in future studies. An *in vitro* study showed that over-expression of GALNT3 resulted in good cardioprotective activity. It was explained that induction of overexpression of GALNT3 in human aortic smooth muscle cells (HASMC) improved vascular calcification due to high phosphate induction by reducing the amount of oxidative stress, reducing inflammation in the vessel area, and enhancing calcification through the TNFR1/NF-κB signaling pathway.[36] The use of tea and coffee in influencing GALNT3 expression has never been explored further, so these results illustrate that administering green tea and coffee extracts can influence GALNT3 expression.

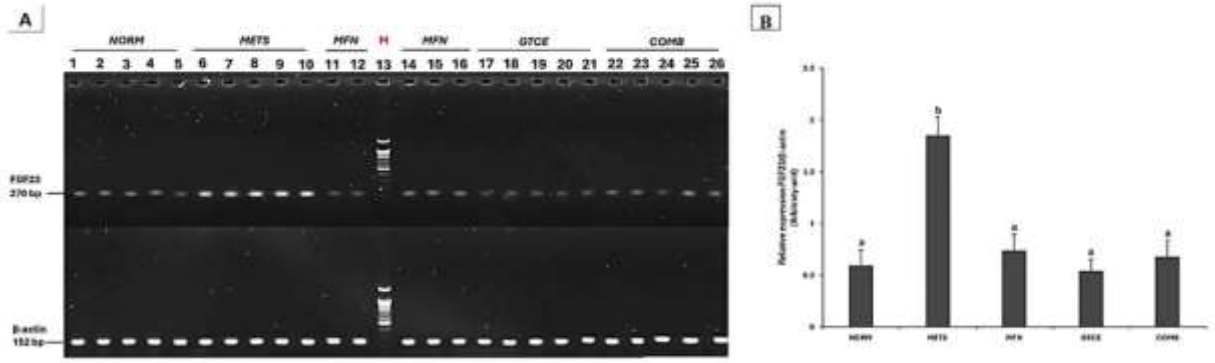

Figure 2: Results of FGF23 gene expression analysis by agarose electrophoresis (A), densitometric analysis of FGF23/*β*-actin expression comparing with *β*-actin (B); DNA Ladder marker (M), negative control (NORM), positive control (METS), metformin (MFN), green coffee tea extract (GTCE), combination of coffee and green tea extract + metformin (COMB). Different notations indicate significant differences (p<0.05)

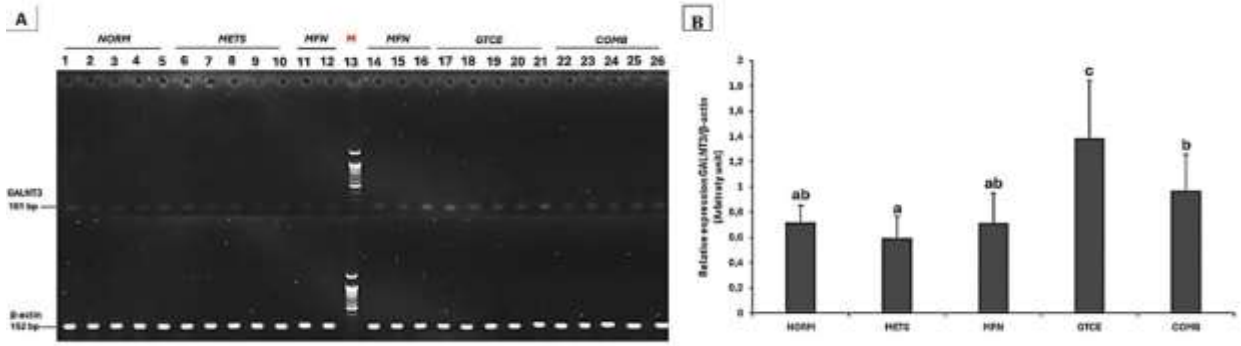

Figure 3: Results of GALNT3 gene expression analysis by agarose electrophoresis (A), densitometric analysis of GALNT3/*β*-actin expression comparing with *β*-actin (B); DNA Ladder marker (M), negative control (NORM), positive control (METS), metformin (MFN), green coffee tea extract (GTCE), combination of coffee and green tea extract + metformin (COMB). Different notations indicate significant differences (p<0.05).

Measurement of RUNX mRNA Expression

Densitometry analysis using ImageJ software revealed increased expression of RUNX2 (RUNX2/*β*-actin) in the METS group, with an average of 9.313 ± 0.511, compared to the NORM group, which had an average of 3.494 ± 0.450. The MFN group showed better RUNX2 expression in the therapy groups than in the METS group, 4.337 ± 0.828. The GTCE group exhibited a significant decrease in mRNA expression, with an average of 2.716 ± 0.482. In contrast, the COMB group had an average of 7.325 ± 0.899, significantly different from the METS group, but was not more effective than GTCE. Statistic analysis showed that the METS group had significantly different results from the other groups (Figure 4B). One of the transcription factors involved in ECM remodeling and increased aortic stiffness, RUNX2, is commonly seen in diabetes mellitus patients.[16] RUNX2 is often found in metabolic syndrome because it can negatively regulate the expression of SIRT6, a protein that controls oxygen use by mitochondria. This regulation leads to a decrease in mitochondrial phosphorylation, which can result in various metabolic disorders in the body.[37] This study found increased RUNX2 expression in the METS group (Figure 4A-B). Administration of single therapies (MFN and GTCE) or combination therapy (COMB) decreased RUNX2 expression compared to METS. However, the COMB group showed higher expression than the GTCE monotherapy group, possibly due to an antagonistic effect of metformin when interacting with active compounds from tea and coffee. Several studies have reported an antagonistic effect of metformin and various active herbal active compounds. One study demonstrated that administering metformin and Gymnema tea to chemically induced diabetic rat models resulted in lower plasma metformin concentrations and significantly higher blood sugar levels.[38] This expression is also possible due to the antagonistic effect of metformin, EGCG, and CGA in this study's green tea and coffee extracts. The antagonistic nature of EGCG was observed in a study conducted by Johnston et al.,[39] where

decaffeinated coffee significantly increased Glucagon-like peptide (GLP-1) expression. This suggests that CGA may antagonize glucose transport. Metformin also alters the Nrf2 signaling pathway of EGCG by activating Sirtuin 1 (SIRT1), which affects Nrf2. Therefore, metformin may reduce the efficacy of EGCG in some situations[40]. This could explain why the decrease in RUNX2 expression in the COMB group was less pronounced. The decrease in RUNX2 expression after metformin therapy is associated with a protective effect against vascular calcification by regulating RUNX2 degradation through the autophagy mechanism on the p62 receptor.[41] The decrease in RUNX2 expression in metabolic syndrome conditions remains limited. Nevertheless, several studies have shown the good anti-inflammatory ability of tea and coffee extracts in reducing RUNX2 expression. Another study showed that EGCG can inhibit the inflammatory process and suppress the Wnt/*β*-Catenin/COX-2 signaling pathway. In contrast, CGA reduces that it can reduce osteogenic genes such as RUNX2 by decreasing the amount of ROS.[42,43]

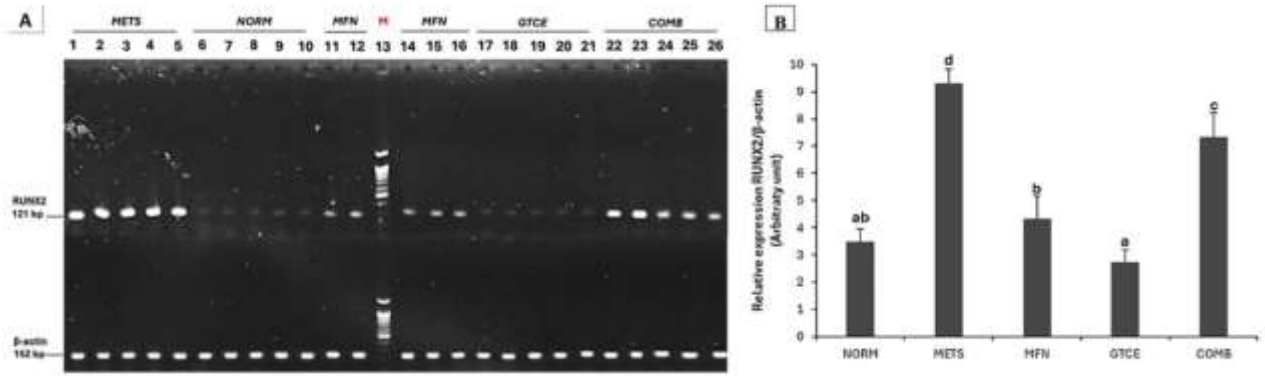

Figure 4: Results of RUNX2 gene expression analysis by agarose electrophoresis (A), densitometric analysis of RUNX2/*β*-actin expression (B); DNA Ladder marker (M), negative control (NORM), positive control (METS), metformin (MFN), green coffee tea extract (GTCE), combination of coffee and green tea extract + metformin (COMB). Different notations indicate significant differences ($p<0.05$)

Correlation Test of Collagen Deposition Area with FGF23, GALNT3, and RUNX2 mRNA Gene Expression

Pearson's correlation test was performed using Pearson's method to evaluate the correlation between gene expression and collagen deposition in the perivascular area of the rat heart (Table 2). FGF23 expression showed a moderately significant correlation ($p<0.05$) with collagen deposition, with a correlation coefficient of 0.801, indicating that higher FGF23 expression was associated with increased collagen deposition. GALNT3 expression, however, did not show a significant correlation with collagen deposition ($p>0.05$), with a correlation coefficient of -0.372, suggesting no relationship between GALNT3 expression and collagen accumulation.

Table 2: Pearson correlation test results between the percentage of collagen deposition area and mRNA, FGF23, GALNT3, and RUNX2 expression.

		Collagen	**FGF23**	**GALNT3**	**RUNX2**
Collagen (%)	Pearson Correlation	1	.603**	-.163	.724**
	Sig. (2-tailed)		.001	.436	.000
	N	25	25	25	25

**Correlation is significant at the 0.01 level (2-tailed)

RUNX2 expression was strongly correlated with collagen deposition ($p<0.05$) with a correlation coefficient of 0.724, indicating that higher RUNX2 expression led to greater collagen deposition. Finally, a significant and positive correlation was observed between FGF23 and RUNX2 expression ($p<0.05$), with a correlation coefficient of 0.664, indicating that higher FGF23 expression was associated with higher RUNX2 expression (Table 3).

Table 3: Pearson correlation test results between FGF23 mRNA expression and RUNX2

		RUNX2	**FGF23**
FGF23	Pearson Correlation	.664**	1
	Sig. (2-tailed)	.000	
	N	25	25
RUNX2	Pearson Correlation	1	.664**
	Sig. (2-tailed)		.000
	N	25	25

**Correlation is significant at the 0.01 level (2-tailed)

Green tea and green coffee extracts have been widely explored as alternative treatments for cardiac fibrosis, offering potential benefits over chemical drugs with known side effects. EGCG, in animal models of heart failure, improved myocardial damage and inhibited heart failure development, likely through fibrosis inhibition and reduced collagen remodeling in the ventricles via the TGF-*β*1/Smad3 pathway.[44] EGCG is also known to be able to improve hypertrophy and fibrosis in the myocardium caused by transverse-aortic constriction through inhibition of the Akt-mTOR pathway.[45] Previous research using decaffeinated tea and coffee extracts showed reduced expression of inflammatory and pro-fibrotic genes such as NF-κB, TNF-α, IL-6, Tgf-*β*1, Rac-1, and α-SMA, which contribute to cardiac fibrosis.[24] Other studies also found that these extracts improved cardiac fibrosis by inhibiting activin-a and collagen-1 genes.[46] Beyond the benefits of green tea and coffee, compounds derived from *Moringa oleifera* and *Elephantopus scaber* have shown promise in reducing the expression of pro-inflammatory genes like TGF-β1 and NF-κB, which are closely linked to fibrosis development.[47,48] This study supports these findings, highlighting the potential of green tea and coffee compounds, particularly CGA and EGCG, in reducing FGF23 and RUNX2 expression in metabolic syndrome due to their anti-inflammatory properties.

Conclusion

Decaffeinated green tea and coffee extracts demonstrate antifibrotic effects by reducing collagen deposition in perivascular fibrosis associated with metabolic syndrome. Compounds such as CGA and EGCG, with potent anti-inflammatory properties, regulate pro-fibrotic genes such as FGF23 and RUNX2 by improving metabolic signaling and reducing inflammation caused by metabolic syndrome.

Conflict of Interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

This research was funded by Professor Grant of the Faculty of Medicine, Universitas Brawijaya, with number 02091/1/UN.10.F0701/T/PT.01.05.1/2024.

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