



Original Article

Asian Pacific Journal of Tropical Biomedicine



apjtb.org

doi: 10.4103/apjtb.apjtb_1_26

Curcumin protects against pressure overload–induced heart failure *via* epigenetic modulation of the Sfrp1/Wnt/ β -catenin pathwayNa Chao¹, Xi-Qiang Wang¹, Wei Wu¹, Ni He^{1,2}, Han-Xiu Liu^{1,2}, Hao-Yang Wang^{1,2}, Jie Zhou^{1,3}, Min-Na Hou⁴✉, Zhong-Wei Liu¹✉¹Department of Cardiology, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi Province, China²School of Medicine, Yan'an University, Yan'an, Shaanxi Province, China³Graduate School, Xi'an Medical University, Xi'an, Shaanxi Province, China⁴Endoscopy Center, Shaanxi Provincial People's Hospital, Xi'an, Shaanxi Province, China

ABSTRACT

Objective: To explore whether curcumin alleviates transverse aortic constriction (TAC)-induced heart failure by modulating the DNMT-Sfrp1-Wnt/ β -catenin signaling.

Methods: Male C57BL/6J mice underwent TAC or sham surgery and then received vehicle or curcumin at 50, 100, or 200 mg/kg/day for 4 weeks. Cardiac structure and performance were evaluated by echocardiography together with invasive hemodynamics, while apoptosis, DNMT activity, *Sfrp1* promoter methylation, and Wnt/ β -catenin signaling were examined using TUNEL staining, bisulfite sequencing, quantitative RT-PCR, and Western blotting.

Results: Compared with untreated TAC mice, curcumin preserved left ventricular systolic function, lowered NT-proBNP, and mitigated ventricular enlargement. It also reduced cardiomyocyte apoptosis, decreased Bax and cleaved caspase-3, and increased Bcl-2. Furthermore, curcumin downregulated Dnmt1, Dnmt3a, and Dnmt3b, reduced total DNMT activity, alleviated methylation of the *Sfrp1* promoter, restored Sfrp1 expression, and diminished nuclear β -catenin as well as c-Myc and cyclin D1.

Conclusions: Curcumin mitigates TAC-induced cardiac dysfunction and adverse remodeling by modulating the DNMT-Sfrp1-Wnt/ β -catenin pathway. These data indicate that curcumin may act as an epigenetic regulator in pathological cardiac remodeling.

KEYWORDS: Curcumin; DNA methyltransferase; Sfrp1; Wnt/ β -catenin signaling; Transverse aortic constriction; Heart failure

1. Introduction

Heart failure (HF) imposes a major global health burden, affecting over 60 million individuals and contributing substantially to death, hospitalization, and healthcare utilization[1]. Chronic pressure overload, as observed in conditions such as long-standing

Summary

Question: Can curcumin ameliorate pressure overload-induced heart failure by regulating DNMT-mediated methylation of *Sfrp1* and the downstream Wnt/ β -catenin cascade?

Findings: In a mouse model of transverse aortic constriction-induced heart failure, curcumin improved ventricular systolic performance, lowered NT-proBNP, reduced cardiomyocyte apoptosis, suppressed Dnmt1, Dnmt3a, and Dnmt3b expression as well as total DNMT activity, decreased methylation of the *Sfrp1* promoter, and inhibited nuclear β -catenin signaling.

Meaning: Curcumin may alleviate pressure overload-associated cardiac remodeling by epigenetically modulating the Sfrp1-dependent Wnt/ β -catenin pathway.

✉To whom correspondence may be addressed. E-mail: liuzhongwei@spph-sx.ac.cn (ZW. Liu); 263304023@qq.com (MN. Hou)

This is an open access article distributed under the terms of the Creative Commons Attribution-Non-Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

For reprints contact: reprints@medknow.com

©2026 Asian Pacific Journal of Tropical Biomedicine Produced by Wolters Kluwer-Medknow.

How to cite this article: Chao N, Wang XQ, Wu W, He N, Liu HX, Wang HY, et al. Curcumin protects against pressure overload-induced heart failure *via* epigenetic modulation of the Sfrp1/Wnt/ β -catenin pathway. Asian Pac J Trop Biomed 2026; 16(7): 297-305.

Article history: Received 1 January 2026; Revision 16 March 2026; Accepted 27 April 2026; Available online 3 July 2026

hypertension or aortic stenosis, is a major cause of pathological ventricular remodeling and ultimately leads to HF[2]. Despite major advances in neurohormonal blockade, a considerable proportion of patients still deteriorate, highlighting the need for therapies that target additional disease mechanisms.

Transverse aortic constriction (TAC) is a well-established murine model of pressure overload-induced HF[3]. Within this context, activation of the Wnt/ β -catenin pathway has been implicated in fibrosis, cardiomyocyte loss, and maladaptive ventricular remodeling[4,5]. Secreted frizzled-related protein 1 (Sfrp1) acts as a decoy antagonist for Wnt ligands, and forced expression of Sfrp1 has been reported to ameliorate TAC-induced ventricular dysfunction and myocardial apoptosis[6]. Nevertheless, the basis for Sfrp1 downregulation in overloaded hearts remains uncertain.

Epigenetic mechanisms, especially DNA methylation, are now recognized as important regulators of cardiovascular gene expression and HF progression[7]. DNMT1, DNMT3a, and DNMT3b mediate cytosine methylation at CpG-rich sites and can silence transcription when promoter methylation increases[8]. In other pathological settings, hypermethylation of the *Sfrp1* promoter has been linked to gene repression, raising the possibility that loss of this endogenous Wnt brake may facilitate pathway overactivation[9].

Curcumin, a bioactive polyphenol from *Curcuma longa*, shows anti-inflammatory, antioxidant, and antifibrotic properties[10]. Beyond these actions, accumulating work indicates that curcumin can modulate DNA methylation by inhibiting DNMT activity and reversing abnormal promoter hypermethylation[11–13]. Whether such epigenetic effects participate in protection against pressure overload-induced HF remains unknown. This study, therefore, aimed to investigate the effect of curcumin against TAC-induced HF and elucidate its underlying mechanisms.

2. Methods

2.1. Animal model of pressure overload and curcumin administration

Male C57BL/6J mice aged 8–10 weeks (22–25 g; Beijing Vital River Laboratory Animal Technology Co., Ltd., China) were maintained under specific pathogen-free conditions at $(22 \pm 2)^\circ\text{C}$ and $(55 \pm 5)\%$ humidity on a 12-h light/dark schedule with *ad libitum* access to food and water.

Pressure overload-induced HF was produced by TAC using a published protocol[14]. Under 2% isoflurane anesthesia, mice were intubated and mechanically ventilated (tidal volume 0.3 mL, respiratory rate 120 breaths/min). Following midline sternotomy, the transverse aorta between the innominate artery and the left common

carotid artery was exposed and tied with a 7-0 silk suture against a 27-gauge blunt needle; the needle was then withdrawn to create a uniform constriction. Sham mice underwent the same operation without aortic ligation.

The dosing regimen was based on a previous report[15] with minor adjustments. Curcumin (purity $\geq 94\%$; Sigma-Aldrich, USA) was suspended in 0.5% carboxymethylcellulose and administered once daily by oral gavage for 4 weeks, starting 24 h after surgery. Animals were randomly assigned to Sham, TAC+Vehicle, TAC+Cur-Low (50 mg/kg/day), TAC+Cur-Med (100 mg/kg/day), or TAC+Cur-High (200 mg/kg/day) groups. The gavage volume was 0.1 mL per 10 g body weight in all groups; Mice in the Sham and TAC+Vehicle groups received vehicle alone. Body weight, food intake, and general condition were recorded twice weekly.

2.2. Invasive hemodynamic assessment

After 4 weeks of treatment, invasive hemodynamic testing was performed to characterize left ventricular function as described previously[16]. Mice were anesthetized with 1.5%–2.0% isoflurane in oxygen and placed on a heated operating pad to maintain core temperature at 37°C . Following tracheal intubation and ventilation, a 1.2 F microtip pressure-volume catheter (Millar Instruments, Houston, TX, USA) was inserted through the right carotid artery and advanced into the left ventricle while pressure waveforms were continuously monitored.

After a 5-min stabilization interval, steady-state pressure-volume loops were collected with a PowerLab system (ADInstruments, Castle Hill, Australia) using LabChart Pro software. Left ventricular systolic pressure, as well as the maximal rates of pressure rise ($+dP/dt_{\text{max}}$) and fall ($-dP/dt_{\text{max}}$) were recorded. For each animal, at least 3 consecutive cardiac cycles were analyzed and averaged for statistical evaluation.

2.3. Echocardiographic analysis of cardiac function

Transthoracic echocardiography was carried out 1 day before terminal hemodynamic testing to assess cardiac geometry and systolic performance as previously reported[17]. Mice were lightly anesthetized with 1.0%–1.5% isoflurane to maintain heart rates of 450–550 beats/min and positioned supine on a heated platform. After hair removal with depilatory cream, prewarmed ultrasound gel was applied to ensure adequate acoustic coupling.

Two-dimensional and M-mode images were acquired with a Vevo 2100 high-frequency imaging system (VisualSonics, Toronto, Canada) equipped with a 30-MHz linear-array transducer. Parasternal long-axis and mid-papillary short-axis views were recorded. Left ventricular end-diastolic diameter, left ventricular end-systolic

diameter, fractional shortening, and ejection fraction were measured from M-mode traces. Values were averaged over 3 consecutive beats and analyzed offline by an investigator blinded to group assignment.

2.4. Measurement of plasma NT-proBNP levels

At the end of the experiment, 0.5–0.8 mL of blood was collected either from the retro-orbital plexus under light anesthesia or by cardiac puncture immediately after hemodynamic assessment. Samples were placed in EDTA tubes containing aprotinin (500 KIU/mL), centrifuged at 3000 $\times g$ for 15 min at 4 °C, and the plasma was stored at –80 °C without repeated freeze-thawing. NT-proBNP concentrations were measured in duplicate using a mouse-specific ELISA kit (Elabscience Biotechnology Co., Ltd., Wuhan, China; 31.25–2000 pg/mL) according to the manufacturer's instructions, and concentrations were calculated from the standard curve.

2.5. Detection of cardiomyocyte apoptosis by terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) staining

Cardiomyocyte apoptosis in left ventricular tissue was assessed by TUNEL. Hearts were arrested in diastole with 10% potassium chloride, excised, rinsed in cold phosphate-buffered saline, and fixed overnight in 4% paraformaldehyde at 4 °C. After dehydration and paraffin embedding, 5- μ m transverse sections from the mid-ventricular level were prepared. TUNEL staining was performed with an *in situ* cell death detection kit (Roche Diagnostics GmbH, Mannheim, Germany) following the manufacturer's instructions. Sections were deparaffinized, rehydrated, treated with proteinase K (20 μ g/mL) for 15 min at room temperature, and incubated with TUNEL reaction mixture at 37 °C for 60 min in a humidified chamber. Nuclei were counterstained with 4',6-diamidino-2-phenylindole (DAPI; Sigma-Aldrich, USA). Five randomly selected fields per section were imaged using a fluorescence microscope (Olympus IX73, Tokyo, Japan) at $\times 400$ magnification. The apoptotic index was calculated as the proportion of TUNEL-positive nuclei among total nuclei.

2.6. Bisulfite sequencing of the *Sfrp1* promoter

Genomic DNA was isolated from frozen left ventricular tissue with the TIANamp Genomic DNA Kit (Tiangen Biotech, Beijing, China). DNA quantity and purity were assessed using a NanoDrop 2000 spectrophotometer, and only samples with A260/A280 values of 1.8–2.0 were used. Bisulfite conversion was performed with the EZ DNA Methylation-Gold Kit (Zymo Research, Irvine, CA, USA). The murine *Sfrp1* promoter CpG island upstream of the transcription

start site was amplified by nested PCR with bisulfite-specific primers designed by MethPrimer to avoid CpG sites within primer regions. Primer sequences are provided in Table 1. PCR products were purified, cloned into pMD19-T, and at least 10 independent clones from each sample were analyzed by Sanger sequencing. CpG methylation patterns were evaluated using QUMA.

2.7. Assay of DNMT enzymatic activity

Nuclear extracts were prepared from frozen left ventricular tissue according to the manufacturer's instructions. Total DNMT activity was measured using the ELISA-based EpiQuik DNA Methyltransferase Activity/Inhibition Assay Kit (Epigentek, Farmingdale, NY, USA), which quantifies methyl group transfer from S-adenosyl-L-methionine to an immobilized DNA substrate. Briefly, 10–20 μ g nuclear protein was added to each well and incubated with reaction buffer at 37 °C for 1 h, followed by capture and detection antibodies as specified by the kit protocol. Absorbance was read at 450 nm on a SpectraMax M5 microplate reader (Molecular Devices, USA). DNMT activity was derived from the standard curve and expressed as OD units/h/mg protein.

2.8. Quantitative real-time polymerase chain reaction (RT-PCR) analysis

Total RNA was extracted from frozen left ventricular tissue with TRIzol reagent (Invitrogen, Carlsbad, CA, USA) in accordance with the manufacturer's protocol. RNA purity and concentration were measured with a NanoDrop 2000 spectrophotometer, and integrity was verified by agarose gel electrophoresis. One microgram of RNA was reverse transcribed using the PrimeScript RT reagent kit (Takara Bio, Shiga, Japan) with random primers. Quantitative real-time PCR was performed on a StepOnePlus Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) using TB Green Premix Ex Taq II (Takara Bio) under the following conditions: 95 °C for 30 s, then 40 cycles of 95 °C for 5 s and 60 °C for 30 s. Relative mRNA levels of *Dnmt1*, *Dnmt3a*, *Dnmt3b*, *Sfrp1*, *c-Myc*, *cyclin D1*, *Bax*, and *Bcl-2* were normalized to *Gapdh*. Primer sequences are shown in Table 2. All samples were run in triplicate, and the expression was calculated by the $2^{-\Delta\Delta Ct}$ method.

Table 1. Bisulfite-specific primer sequences.

Primer name	Primer sequence
Bisulfite-specific outer primer	Forward: 5'-TTGGGTTTTAGTTTTAGTTAGGTT-3'
	Reverse: 5'-CACCTACTCTCAAACCTCACTAAAA-3'
Nested inner primer	Forward: 5'-GGGTTTTAGTTTTAGTTAGGTTTT-3'
	Reverse: 5'-TCAAACCTCACTAAAACTTACCCC-3'

Table 2. Primer sequences for quantitative RT-PCR.

Gene	Primer sequence
<i>Dnmt1</i>	Forward: 5'-GGACAAGGAGAATGCCATGAAGC-3' Reverse: 5'-TTACTCCGTCCAGTGCCACCAA-3'
<i>Dnmt3a</i>	Forward: 5'-CGCAAAGCCATCTACGAAGTCC-3' Reverse: 5'-GCTTGTCTGCACTTCCACAGC-3'
<i>Dnmt3b</i>	Forward: 5'-CGCACAACCAATGACTCTGCTG-3' Reverse: 5'-GGTGACTTCAGAAGCCATCCGT-3'
<i>Sfrp1</i>	Forward: 5'-CAATACCACGGAAGCCTCTAAGC-3' Reverse: 5'-GCAAACCTCGCTTGACAGAGATG-3'
<i>c-Myc</i>	Forward: 5'-TCGCTGCTGTCCTCCGAGTCC-3' Reverse: 5'-GGTTTGCCTCTTCTCCACAGAC-3'
<i>Cnd1 (Cyclin D1)</i>	Forward: 5'-GCAGAAGGAGATTGTGCCATCC-3' Reverse: 5'-AGGAAGCGGTCCAGGTAGTTCA-3'
<i>Bax</i>	Forward: 5'-AGGATGCGTCCACCAAGAAG-3' Reverse: 5'-TCCGTGTCCACGTACGAATCA-3'
<i>Bcl-2</i>	Forward: 5'-CCTGTGGATGACTGAGTACCTG-3' Reverse: 5'-AGCCAGGAGAAATCAAACAGAGG-3'
<i>Gapdh</i>	Forward: 5'-CATCACTGCCACCCAGAAGACTG-3' Reverse: 5'-ATGCCAGTGAGCTTCCCGTTCAG-3'

2.9. Western blot analysis

Frozen left ventricular tissue was homogenized in ice-cold RIPA buffer (Beyotime, Shanghai, China) containing protease and phosphatase inhibitors (Roche, Basel, Switzerland). After centrifugation, protein concentration was determined by BCA assay. Equal amounts of protein (30-50 µg) were separated by 8%-12% SDS-PAGE and transferred to PVDF membranes. Membranes were blocked for 1 h at room temperature in 5% non-fat milk/TBST and incubated overnight at 4°C with primary antibodies against DNMT1 (D63A6, CST, 1:1 000), DNMT3a (D23G1, CST, 1:1 000), DNMT3b (CST, 1:1 000), Sfrp1 (EPR23092-253, Abcam, 1:1 000), total β-catenin (D10A8, CST, 1:1 000), active β-catenin (D13A1, CST, 1:1 000), c-Myc (D84C12, CST, 1:1 000), cyclin D1 (92G2, CST, 1:1 000), cleaved caspase-3 (Asp175, CST, 1:1 000), Bax (D2E11, CST, 1:1 000), Bcl-2 (D55G8, CST, 1:1 000), GAPDH (14C10, CST, 1:1 000), and Histone H3 (D1H2, CST, 1:2 000). Membranes were then incubated with HRP-conjugated secondary antibodies according to the manufacturer’s protocol. Bands were visualized with ECL substrate (Thermo Fisher Scientific) and quantified in ImageJ after normalization to GAPDH or Histone H3, as appropriate.

2.10. Statistical analysis

Data are expressed as mean ± SD. Normality was evaluated with the Shapiro-Wilk test. Differences among multiple groups were analyzed by one-way ANOVA followed by Tukey’s *post hoc* test. A two-sided *P* value < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA).

2.11. Ethical statement

All procedures were approved by the Institutional Animal Care and Use Committee of Shaanxi Provincial People’s Hospital (Approval No. 2024K-165; approval date: 30 August 2024) and complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

3. Results

3.1. Curcumin preserves ventricular function and restrains remodeling after TAC

Cardiac function was assessed 4 weeks after TAC by echocardiography and invasive hemodynamics. Representative M-mode images are presented in Figure 1A. Compared with sham-operated mice, TAC markedly decreased left ventricular ejection fraction and fractional shortening while increasing left ventricular end-diastolic diameter and left ventricular end-systolic diameter (*P*<0.05, Figure 1B-E). Curcumin treatment significantly preserved systolic performance and reduced chamber dilatation (*P*<0.05), with the medium- and high-dose groups showing greater benefit than the low-dose group. Invasive hemodynamic findings were consistent with the echocardiographic data (Figure 1F-H). TAC caused significant changes on left ventricular systolic pressure, +dP/dtmax and -dP/dtmax, whereas curcumin partially normalized these parameters (*P*<0.05). Plasma NT-proBNP, an indicator of HF severity, was markedly increased after TAC (*P*<0.05) and declined dose-dependently with curcumin administration (*P*<0.05, Figure 1I).

3.2. Curcumin inhibits cardiomyocyte apoptosis in pressure overload-induced HF

TUNEL staining of left ventricular sections revealed a pronounced rise in apoptotic nuclei after TAC compared with sham operation (*P*<0.05, Figure 2A-B). Curcumin treatment significantly reduced the percentage of TUNEL-positive cardiomyocytes in a dose-dependent fashion (*P*<0.05), with values in the high-dose group approaching those of sham mice. Western blot analysis showed a similar pattern for apoptosis-related proteins (Figure 2C-G): TAC notably increased Bax and cleaved caspase-3 expressions, and reduced Bcl-2 expression (*P*<0.05), whereas curcumin largely reversed these changes (*P*<0.05). Consistent with the protein findings, quantitative RT-PCR analysis further demonstrated that TAC significantly upregulated *Bax* mRNA and downregulated *Bcl-2* mRNA compared with sham mice (*P*<0.05, Figure 2H-I). Curcumin treatment dose-dependently reversed these transcriptional alterations, as evidenced

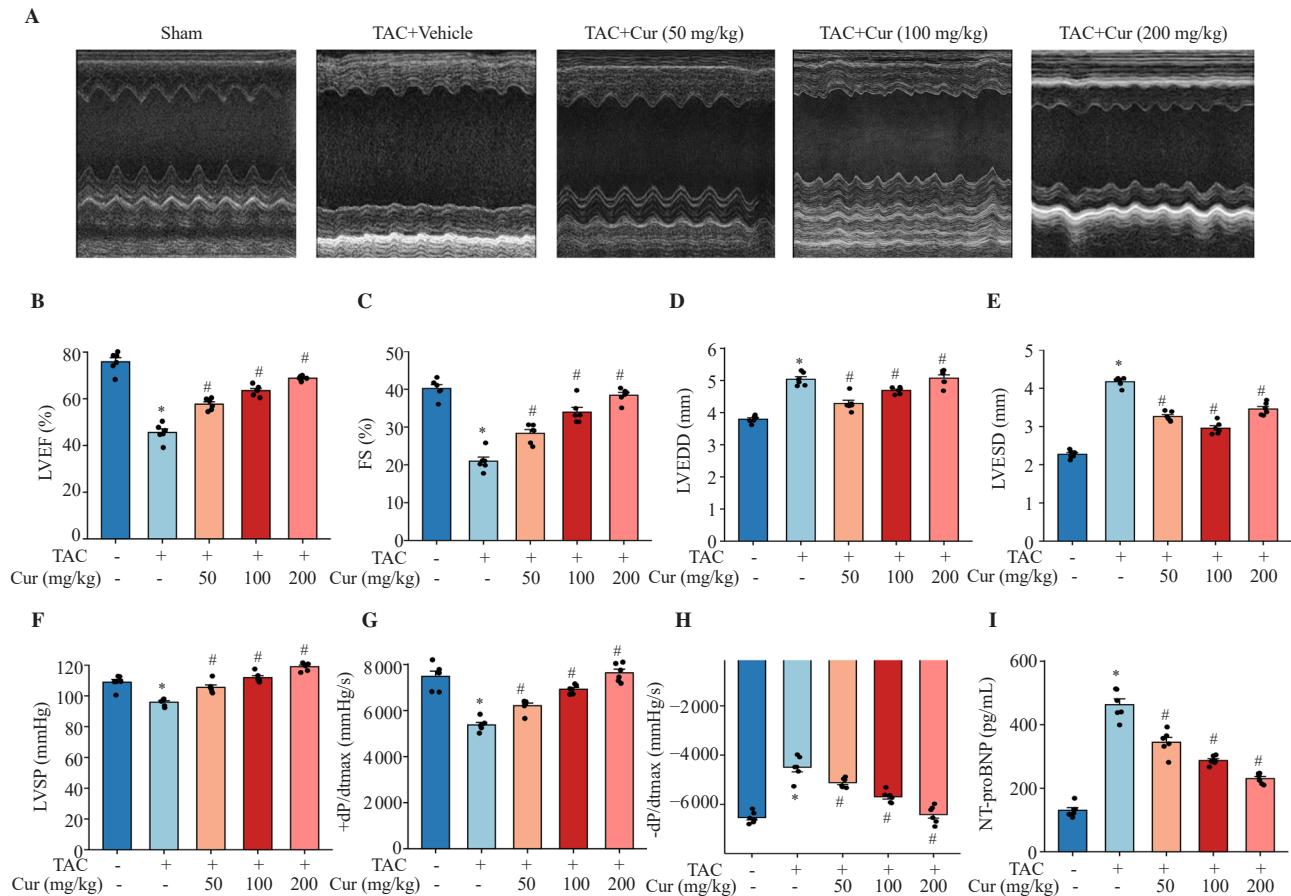


Figure 1. Curcumin preserves cardiac function and reduces ventricular remodeling after transverse aortic constriction (TAC). (A) Representative M-mode echocardiograms obtained 4 weeks after TAC in different groups. (B-E) Quantification of left ventricular ejection fraction (LVEF), fractional shortening (FS), left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD). (F-H) Invasive hemodynamic measurements including left ventricular systolic pressure (LVSP), as well as maximal rates of pressure rise (+dP/dtmax) and fall (-dP/dtmax). (I) Plasma NT-proBNP concentrations determined by ELISA. Data are shown as mean $\pm$ SD ($n = 6$). One-way ANOVA followed by Tukey's *post hoc* test was used. * $P < 0.05$ versus the Sham group; # $P < 0.05$ versus the TAC+Vehicle group. Cur: Curcumin.

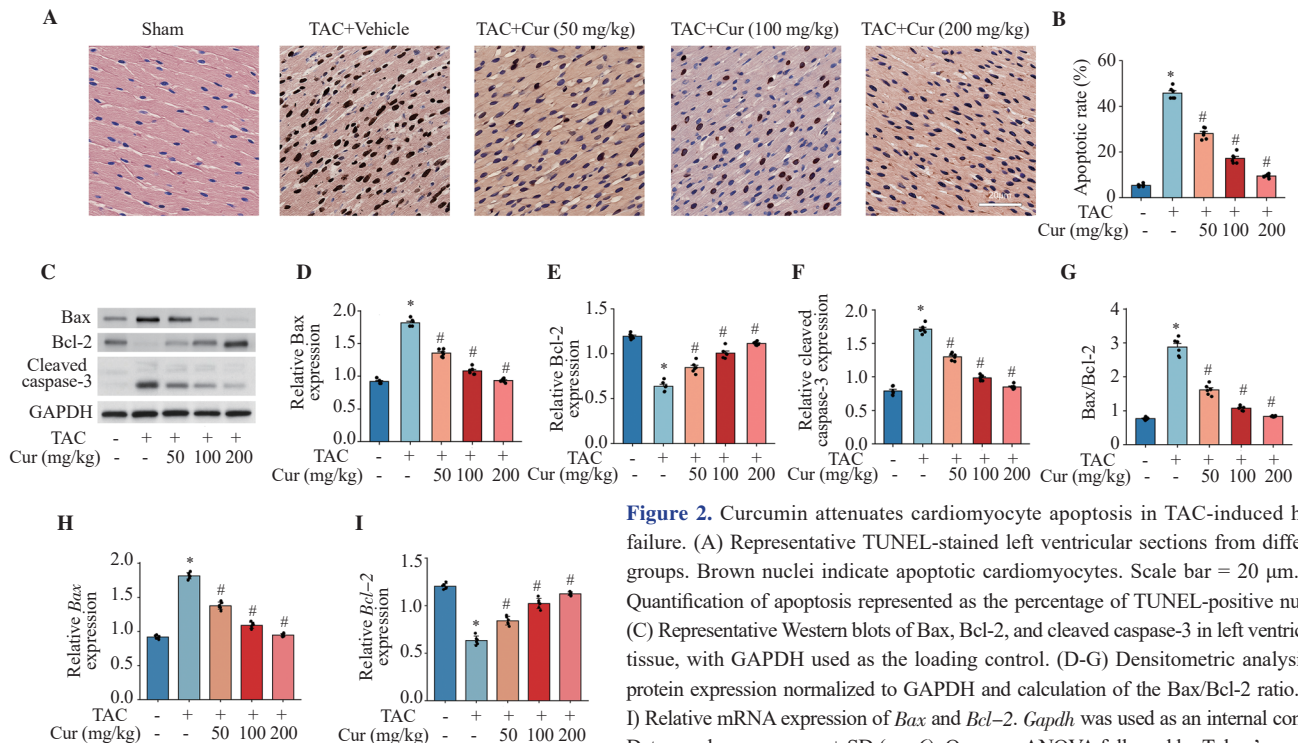


Figure 2. Curcumin attenuates cardiomyocyte apoptosis in TAC-induced heart failure. (A) Representative TUNEL-stained left ventricular sections from different groups. Brown nuclei indicate apoptotic cardiomyocytes. Scale bar = 20 μ m. (B) Quantification of apoptosis represented as the percentage of TUNEL-positive nuclei. (C) Representative Western blots of Bax, Bcl-2, and cleaved caspase-3 in left ventricular tissue, with GAPDH used as the loading control. (D-G) Densitometric analysis of protein expression normalized to GAPDH and calculation of the Bax/Bcl-2 ratio. (H-I) Relative mRNA expression of Bax and Bcl-2. GAPDH was used as an internal control. Data are shown as mean $\pm$ SD ($n = 6$). One-way ANOVA followed by Tukey's *post hoc* test was used. * $P < 0.05$ versus the Sham group; # $P < 0.05$ versus the TAC+Vehicle group.

by markedly decreased *Bax* mRNA levels and increased *Bcl-2* mRNA levels ($P<0.05$, Figure 2H-I).

3.3. Curcumin downregulates DNMT expression and activity, and decreases *Sfrp1* promoter methylation

To determine whether curcumin affects epigenetic regulation under pressure overload, we quantified DNMT expression and activity in left ventricular tissue. TAC significantly upregulated the mRNA

expression of *Dnmt1*, *Dnmt3a*, and *Dnmt3b* ($P<0.05$, Figure 3A-C), and increased the corresponding protein levels ($P<0.05$, Figure 3D-G). However, curcumin markedly downregulated the mRNA and protein expressions of *Dnmt1*, *Dnmt3a*, and *Dnmt3b* in a dose-dependent manner ($P<0.05$). Moreover, total DNMT enzymatic activity was noticeably increased in TAC hearts ($P<0.05$), but lowered after curcumin treatment ($P<0.05$, Figure 3H). Bisulfite sequencing demonstrated greater CpG methylation in the *Sfrp1* promoter after TAC ($P<0.05$), whereas curcumin alleviated this

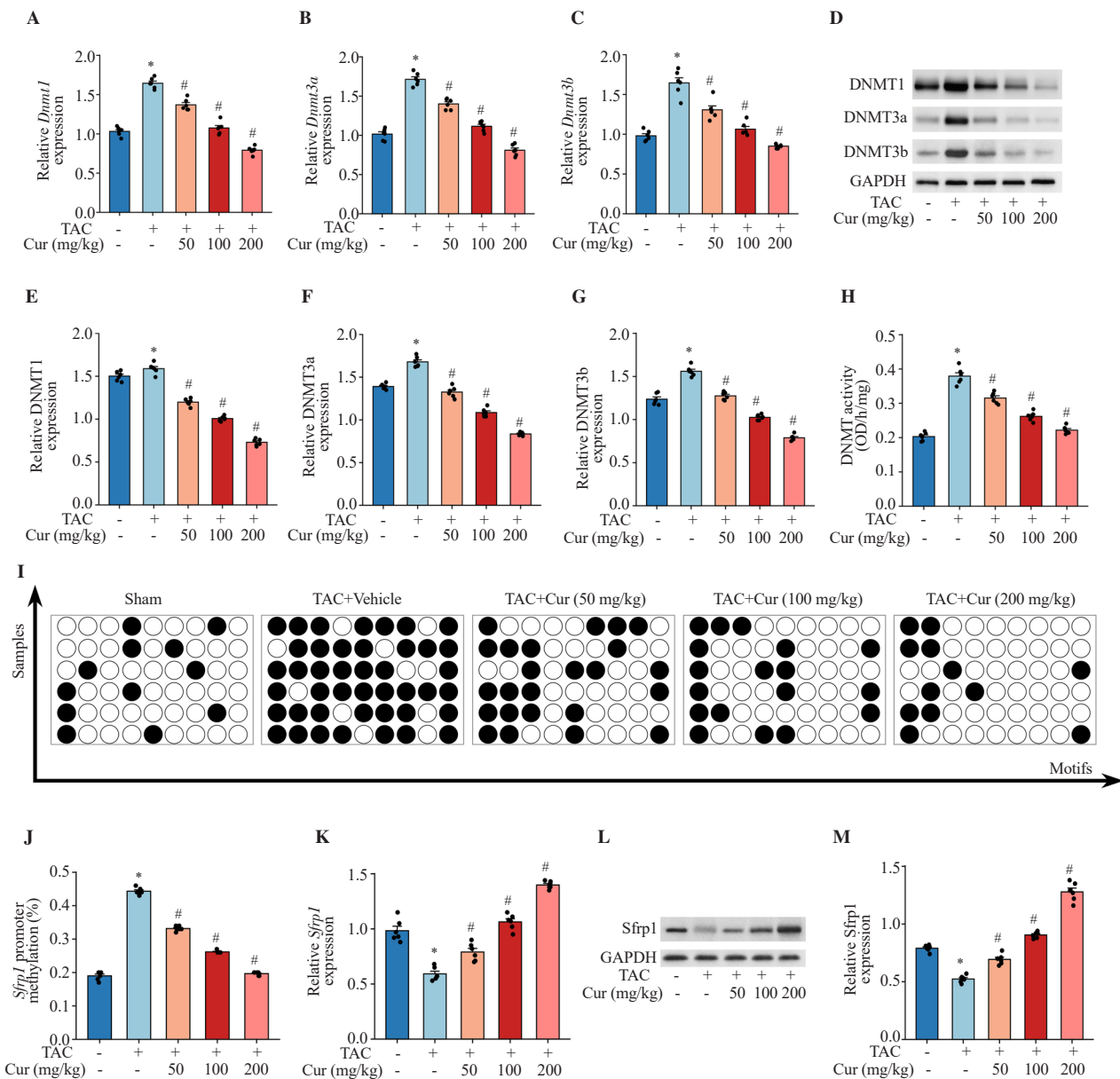


Figure 3. Curcumin decreases DNMT expression and activity, and alleviates *Sfrp1* promoter methylation. (A-C) Relative mRNA levels of *Dnmt1*, *Dnmt3a*, and *Dnmt3b* in left ventricular tissue measured by quantitative RT-PCR. (D) Representative Western blots showing DNMT1, DNMT3a, and DNMT3b protein expression, with GAPDH as the loading control. (E-G) Quantitative analysis of DNMT family proteins normalized to GAPDH. (H) Total DNMT enzymatic activity in nuclear extracts from left ventricular tissue. (I) Bisulfite sequencing PCR analysis of CpG methylation across the *Sfrp1* promoter region; filled circles denote methylated CpG sites and open circles denote unmethylated sites. (J) Quantification of *Sfrp1* promoter methylation. (K) Relative *Sfrp1* mRNA expression quantified by quantitative RT-PCR. (L) Representative Western blot of *Sfrp1* protein expression. (M) Quantification of *Sfrp1* protein expression normalized to GAPDH. Data are shown as mean $\pm$ SD ($n = 6$). One-way ANOVA followed by Tukey's *post hoc* test was used. * $P < 0.05$ versus the Sham group; # $P < 0.05$ versus the TAC+Vehicle group.

increase in methylation ($P < 0.05$, Figure 3I-J). Consistent with these changes, TAC hearts showed markedly decreased mRNA and protein expression of *Sfrp1* ($P < 0.05$), which was restored by curcumin treatment dose-dependently ($P < 0.05$, Figure 3K-M).

3.4. Curcumin dampens Wnt/ β -catenin signaling in pressure-overloaded myocardium

We then evaluated whether curcumin influences the Wnt/ β -catenin signaling in the overloaded heart. TAC caused marked nuclear accumulation of β -catenin, indicating activation of canonical Wnt signaling, whereas curcumin reduced nuclear β -catenin (Figure 4A-B). Downstream targets *c-Myc* and *cyclin D1* followed the same pattern: both mRNA and protein levels were increased by TAC ($P < 0.05$). However, curcumin treatment reversed TAC-induced changes in their expression, returning them to levels comparable to controls ($P < 0.05$, Figure 4C-G).

4. Discussion

This study shows that oral curcumin improves cardiac performance and attenuates adverse remodeling in a mouse model of pressure overload-induced HF. These benefits were accompanied by reduced expression and activity of DNMT1, DNMT3a, and DNMT3b, lower methylation of the *Sfrp1* promoter, improved *Sfrp1* expression, inhibited β -catenin signaling, and reduced cardiomyocyte apoptosis.

Collectively, these observations confirm that curcumin treatment alleviates pressure overload-induced HF by modulating the DNMT-*Sfrp1*-Wnt/ β -catenin axis.

The cardioprotective actions of curcumin have previously been attributed to antioxidant, anti-inflammatory, and antifibrotic effects[18,19]. Our findings expand this framework by suggesting that epigenetic regulation may represent an additional mechanism underlying its myocardial benefits. This interpretation is in line with emerging evidence that DNA methylation is dynamically remodeled during cardiovascular disease progression and HF[7,20,21].

Sfrp1 is an endogenous antagonist of Wnt signaling. In our TAC model, pressure overload increased DNMT expression and total DNMT activity, coinciding with higher methylation of the *Sfrp1* promoter, reduced *Sfrp1* expression, and enhanced nuclear β -catenin signaling. Curcumin reversed these alterations. Although our experiments do not establish direct causality, the overall pattern is consistent with the possibility that curcumin limits Wnt/ β -catenin activation, at least in part, by preserving *Sfrp1* expression[6,22–26].

From a translational standpoint, these data support further exploration of epigenetic approaches that interrupt maladaptive Wnt signaling in HF. Curcumin has pleiotropic biological actions and an encouraging body of preclinical evidence[27], yet its poor oral bioavailability remains an important obstacle[28,29]. Improved formulations or structurally related derivatives may therefore be required before clinical application can be rigorously tested.

Several limitations merit consideration. First, although the data support involvement of the DNMT-*Sfrp1*-Wnt/ β -catenin axis, direct

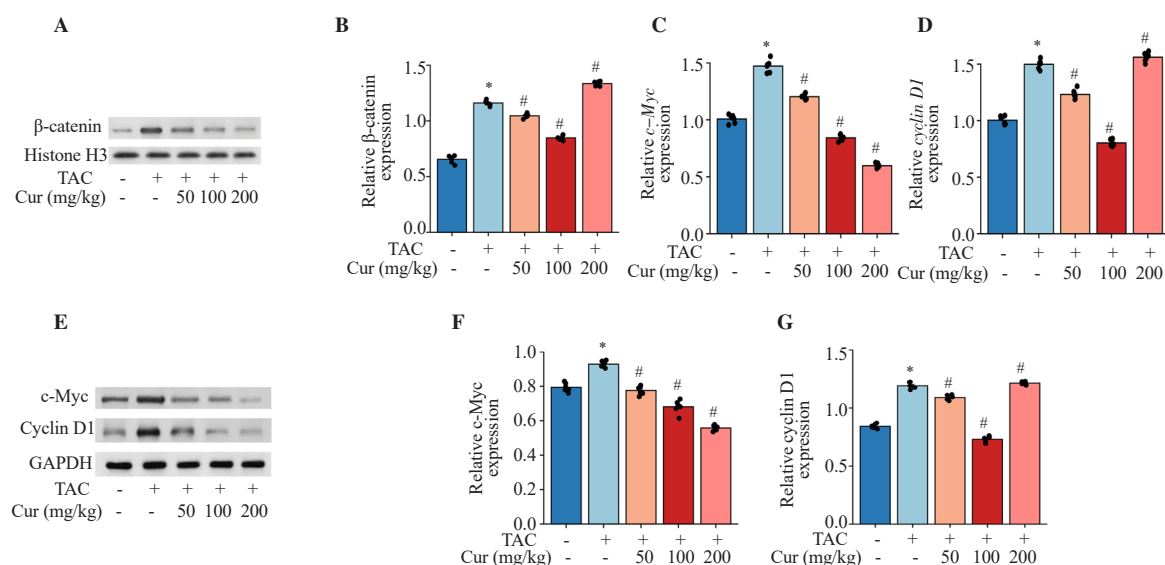


Figure 4. Curcumin inhibits Wnt/ β -catenin activation in pressure-overloaded hearts. (A) Representative Western blots of nuclear β -catenin in left ventricular tissue, with Histone H3 serving as the nuclear loading control. (B) Quantification of nuclear β -catenin normalized to Histone H3. (C-D) Relative mRNA expression of *c-Myc* and *cyclin D1* measured by quantitative RT-PCR. (E) Representative Western blots of *c-Myc* and *cyclin D1* proteins, with GAPDH as the internal control. (F-G) Quantitative analysis of *c-Myc* and *cyclin D1* protein levels normalized to GAPDH. Data are shown as mean $\pm$ SD ($n = 6$). One-way ANOVA followed by Tukey's *post hoc* test was used. * $P < 0.05$ versus the Sham group; # $P < 0.05$ versus the TAC+Vehicle group.

causal validation using Sfrp1 loss-of-function or rescue experiments was not performed. Second, genome-wide methylation profiling was not included, so broader off-target epigenetic effects cannot be ruled out. Third, the observation period was limited to 4 weeks, and longer-term efficacy and safety were not assessed. Future studies should incorporate genetic or pharmacological strategies to directly investigate the roles of Sfrp1 and β -catenin, examine whether the same mechanism operates in other HF settings such as post-infarction remodeling, and determine whether curcumin or optimized derivatives provide an additive benefit to standard HF therapy.

In summary, curcumin mitigated TAC-induced cardiac dysfunction and maladaptive remodeling in mice by lowering DNMT activity, reducing methylation of the *Sfrp1* promoter, upregulating Sfrp1 expression, and inhibiting the Wnt/ β -catenin signaling.

Conflict of interest statement

The authors declare that there is no competing interests.

Funding

This work was supported by the Shaanxi Provincial Traditional Chinese Medicine Science and Technology Innovation Capacity Enhancement Program-Innovation Talent in Traditional Chinese Medicine Research (Grant No. TZKN-CXRC-15) and the Shaanxi Provincial Innovation Capacity Support Program-Science and Technology Innovation Team Project (Grant No. 2025RS-XCTD-053).

Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

ZWL and MNH conceived and designed the study, supervised the project, interpreted the findings, and critically revised the manuscript. NC, XQW, and WW conducted the animal experiments, echocardiographic and hemodynamic evaluations, and participated in data acquisition and interpretation. NH performed molecular and biochemical assays and contributed to data analysis. HXL, HYW, and JZ were responsible for statistical analysis, figure preparation, and interpretation of the results. All authors approved the final

manuscript and agree to be accountable for all aspects of the work.

References

- [1] Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: A comprehensive and updated review of epidemiology. *Cardiovasc Res* 2023; **118**(17): 3272-3287.
- [2] Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *Eur J Heart Fail* 2021; **23**(3): 352-380.
- [3] Bosch L, de Haan JJ, Bastemeijer M, van der Burg J, van der Worp E, Wesseling M, et al. The transverse aortic constriction heart failure animal model: A systematic review and meta-analysis. *Heart Fail Rev* 2021; **26**(6): 1515-1524.
- [4] Bergmann MW. WNT signaling in adult cardiac hypertrophy and remodeling: Lessons learned from cardiac development. *Circ Res* 2010; **107**(10): 1198-1208.
- [5] Zelarayan LC, Noack C, Sekkali B, Kmecova J, Gehrke C, Renger A, et al. Beta-catenin downregulation attenuates ischemic cardiac remodeling through enhanced resident precursor cell differentiation. *Proc Natl Acad Sci U S A* 2008; **105**(50): 19762-19767.
- [6] Pan S, Zhao X, Wang X, Tian X, Wang Y, Fan R, et al. Sfrp1 attenuates TAC-induced cardiac dysfunction by inhibiting Wnt signaling pathway-mediated myocardial apoptosis in mice. *Lipids Health Dis* 2018; **17**: 202.
- [7] Desiderio A, Pastorino M, Campitelli M, Longo M, Miele C, Napoli R, et al. DNA methylation in cardiovascular disease and heart failure: Novel prediction models? *Clin Epigenetics* 2024; **16**. doi: 10.1186/s13148-024-01722-x.
- [8] Lyko F. The DNA methyltransferase family: A versatile toolkit for epigenetic regulation. *Nat Rev Genet* 2018; **19**(2): 81-92.
- [9] Paluszczak J, Hemmerling D, Kostrzewska-Poczekaj M, Jarmuz-Szymczak M, Grenman R, Wierzbicka M, et al. Frequent hypermethylation of WNT pathway genes in laryngeal squamous cell carcinomas. *J Oral Pathol Med* 2014; **43**(9): 652-657.
- [10] Hewlings SJ, Kalman DS. Curcumin: A review of its effects on human health. *Foods* 2017; **6**(10): 92.
- [11] Link A, Balaguer F, Shen Y, Lozano JJ, Leung HC, Boland CR, et al. Curcumin modulates DNA methylation in colorectal cancer cells. *PLoS One* 2013; **8**(2). doi: 10.1371/journal.pone.0057709.
- [12] Divyajanani S, Harithpriya K, Ganesan K, Ramkumar KM. Dietary polyphenols remodel DNA methylation patterns of NRF2 in chronic disease. *Nutrients* 2023; **15**(15): 3347.
- [13] Liu Z, Xie Z, Jones W, Pavlovicz RE, Liu S, Yu J, et al. Curcumin is a potent DNA hypomethylation agent. *Bioorg Med Chem Lett* 2009; **19**(3):

- 706-709.
- [14]Chen X, Zhang Z, Zhang X, Jia Z, Liu J, Chen X, et al. Paeonol attenuates heart failure induced by transverse aortic constriction *via* ERK1/2 signalling. *Pharm Biol* 2022; **60**(1): 562-569.
- [15]Chen Y, Wang J, Jing Z, Ordovas JM, Wang J, Shen L. Anti-fatigue and anti-oxidant effects of curcumin supplementation in exhaustive swimming mice *via* Nrf2/Keap1 signal pathway. *Curr Res Food Sci* 2022; **5**: 1148-1157.
- [16]Maguire ML, McAndrew DJ, Lake HA, Ostrowski PJ, Zervou S, Neubauer S, et al. Synergistic effect on cardiac energetics by targeting the creatine kinase system: *In vivo* application of high-resolution 31P-CMRS in the mouse. *J Cardiovasc Magn Reson* 2023; **25**. doi: 10.1186/s12968-023-00911-6.
- [17]Mattila M, Koskenvuo J, Soderstrom M, Eerola K, Savontaus M. Intramyocardial injection of SERCA2a-expressing lentivirus improves myocardial function in doxorubicin-induced heart failure. *J Gene Med* 2016; **18**(6): 124-133.
- [18]Zeng YF, Guo QH, Wei XY, Chen SY, Deng S, Liu JJ, et al. Cardioprotective effect of curcumin on myocardial ischemia/reperfusion injury: A meta-analysis of preclinical animal studies. *Front Pharmacol* 2023; **14**. doi: 10.3389/fphar.2023.1184292.
- [19]Wang W, Chang P, Jin J, Pu F, Li D, Bai Y, et al. Cardioprotective effects of curcumin against diabetic cardiomyopathies: A systematic review and meta-analysis of preclinical studies. *Phytomedicine* 2024; **129**. doi: 10.1016/j.phymed.2024.155619.
- [20]Movassagh M, Choy MK, Knowles DA, Cordeddu L, Haider S, Down T, et al. Distinct epigenomic features in end-stage failing human hearts. *Circulation* 2011; **124**(22): 2411-2422.
- [21]Haas J, Frese KS, Park YJ, Keller A, Vogel B, Lindroth AM, et al. Alterations in cardiac DNA methylation in human dilated cardiomyopathy. *EMBO Mol Med* 2013; **5**(3): 413-429.
- [22]Horitani K, Shiojima I. Wnt signaling in cardiac development and heart diseases. *In Vitro Cell Dev Biol Anim* 2024; **60**(5): 482-488.
- [23]Baharudin R, Tieng FYF, Lee LH, Ab Mutalib NS. Epigenetics of SFRP1: The dual roles in human cancers. *Cancers (Basel)* 2020; **12**(2). doi: 10.3390/cancers12020445.
- [24]Suzuki H, Watkins DN, Jair KW, Schuebel KE, Markowitz SD, Chen WD, et al. Epigenetic inactivation of SFRP genes allows constitutive WNT signaling in colorectal cancer. *Nat Genet* 2004; **36**(4): 417-422.
- [25]Tao J, Wei X, Huang Y, Liu F, Wu Y, Adi D, et al. Sfrp1 protects against acute myocardial ischemia injury in aged mice by inhibiting the Wnt/ β -catenin signaling pathway. *J Cardiothorac Surg* 2021; **16**: 12. doi: 10.1186/s13019-020-01389-4.
- [26]van de Schans VA, van den Borne SW, Strzelecka AE, Janssen BJ, van der Velden JL, Langen RC, et al. Interruption of Wnt signaling attenuates the onset of pressure overload-induced cardiac hypertrophy. *Hypertension* 2007; **49**(3): 473-480.
- [27]Xiang Y, Lv Y, Liu XX, Li BT, Liu J. Curcumin attenuates pressure overload-induced cardiac fibrosis in mice *via* modulating the miR-29b/HDAC4 axis. *Asian Pac J Trop Biomed* 2026; **16**(2): 59-67.
- [28]Xu Q, Lian H, Zhou R, Gu Z, Wu J, Wu Y, et al. Curcumin and multiple health outcomes: Critical umbrella review of intervention meta-analyses. *Front Pharmacol* 2025; **16**. doi: 10.3389/fphar.2025.1601204.
- [29]Yallapu MM, Jaggi M, Chauhan SC. Curcumin nanoformulations: A future nanomedicine for cancer. *Drug Discov Today* 2012; **17**(1-2): 71-80.

Publisher's note

The Publisher of the *Journal* remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Edited by Liang Q, Tan BJ