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Review Article

# The Effect of Colchicine on Cardiac Dysfunction in Isoproterenol-Induced Mice: Insights into the Role of PGC-1α/PPARα Signaling Pathway

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## Abstract

**Background:** Chronic Heart Failure (CHF) has emerged as a global cardiovascular ailment that poses a significant threat to human life and well-being. The disruption of myocardial energy metabolism serves as a pathological foundation for the onset and progression of CHF. PGC-1α functions as a co-activator of PPARα, a pivotal nuclear transcriptional factor responsible for regulating myocardial energy metabolism. PPARα governs the expression of downstream target genes, namely CPT-1 and MCAD, which are critical rate-limiting enzymes involved in fatty acid β-oxidation. Colchicine, a conventional anti-gout medication, exhibits promising potential in the prevention of cardiovascular diseases. However, further investigation is required to determine whether colchicine can enhance Congestive Heart Failure (CHF) in isoproterenol-induced mice through the up-regulation of the PGC-1α/PPARα signaling pathway and the promotion of myocardial fatty acid β-oxidation.

**Objective:** This study aimed to examine the impact of colchicine on CHF in isoproterenol-induced mice.

**Methods and results:** The results of small animal ultrasound demonstrated that colchicine led to an increase in left ventricular ejection fraction and left ventricular fractional shortening, as well as a decrease in left ventricular end-diastole volume and left ventricular end-systole volume. The H&E staining results demonstrated that the administration of colchicine effectively mitigated the irregular arrangement of myocardial cells, cardiomyocyte hypertrophy, and infiltration of inflammatory cells in mice induced with isoproterenol. Furthermore, the Western blot analysis revealed that colchicine significantly increased the protein expressions of PGC-1α, PPARα, CPT-1α, and MCAD in the left ventricle of the heart. Additionally, the molecular docking results indicated a direct binding between colchicine and PPARα.

**Conclusion:** In conclusion, colchicine exhibits a therapeutic potential in ameliorating cardiac dysfunction in isoproterenol-induced mice, potentially mediated, at least in part, by enhancing the activity of PGC-1α, PPARα, CPT-1α, and MCAD and to enhance the fatty acid β-oxidation.

**Keywords:** Cardiac dysfunction; Chronic heart failure; Colchicine; Isoproterenol; MCAD; PGC-1α; PPARα

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## Introduction

Chronic Heart Failure (CHF) has emerged as a prevalent cardiovascular ailment worldwide, with its morbidity and mortality rates exhibiting a persistent upward trend. This poses a significant threat to human life and well-being [1]. CHF manifests as a clinical syndrome characterized by impaired cardiac systolic and diastolic function, stemming from various etiologies. Consequently, the cardiac output fails to adequately meet the body's metabolic demands, leading to aberrant hemodynamics and activation of the neurohormonal system [2]. Given that the heart serves as a vital organ with substantial energy requirements, disturbances in myocardial energy metabolism serve as a pathological foundation for the onset and progression of CHF [3]. In the initial phase of Congestive Heart Failure (CHF), the utilization rate of fatty acids remains normal or may even increase as a compensatory mechanism [4]. However, as CHF progresses, there is a decline in fatty acid utilization and metabolism, leading to a reduction in ATP production and exacerbating the disorder in myocardial energy metabolism [4].

The PGC-1α/PPARα signaling pathway plays a crucial role in regulating myocardial energy metabolism. Peroxisome Proliferator-Activated Receptors (PPARs), including PPARα, PPARγ, and PPARβ/δ, are nuclear transcription factors [5]. Previous research has shown that PPARα is highly expressed in the heart and primarily involved in regulating fatty, metabolism, and oxidative stress [5,6]. Studies have demonstrated that the activation of PPARα has been found to effectively inhibit myocardial hypertrophy, fibrosis, and ventricular remodeling, thereby leading to an improvement in Congestive Heart Failure (CHF) [7,8]. PGC-1α, acting as a co-activator of PPARα, plays a crucial role in this process. The activation of PPARα

influences myocardial energy metabolism by up-regulating the expression of key rate-limiting enzymes involved in fatty acid β-oxidation, such as carnitine palmitoyltransferase-1 (CPT-1) and Medium-Chain Acyl-CoA Dehydrogenase (MCAD). Consequently, this promotes myocardial fatty acid β-oxidation and regulates the overall process of myocardial energy metabolism [9,10]. Isoproterenol (ISO), a β-adrenergic receptor agonist, has the ability to stimulate increase the heart rate and myocardial contractility. It has been reported that the subcutaneous injection of 5 mg/kg isoproterenol for 14 days can cause the CHF in mice [11,12].

Colchicine, an ancient anti-inflammatory medication, is commonly employed in the clinical management of conditions such as gout, acute pericarditis, and familial Mediterranean fever [13]. The Colchicine cardiovascular outcomes trial has substantiated its efficacy in safeguarding cardiovascular health [14]. Recent clinical trials have demonstrated that colchicine can diminish the likelihood of cardiovascular events in patients undergoing initial treatment for acute myocardial infarction [15]. Nevertheless, the potential of colchicine to enhance congestive heart failure in isoproterenol-induced mice through the up-regulation of the PGC-1α/PPARα signaling pathway and promotion remains uncertain. Thus, this study was designed to explore whether colchicine can alleviate the isoproterenol-induced CHF in mice and to investigate the related mechanism.

## Methods

### Reagent

Colchicine was purchased from Xishuangbanna Banna Pharmaceutical Co., Ltd. (SFDA approval number: H53021369, Yunnan, China). Isoproterenol was purchased from Med Chem Express (purity > 99% as determined by HPLC, batch number: HY- B0468, USA). Colchicine was dissolved in double-distilled water and isoproterenol was dissolved in saline. Near uses presently to match.

### Animals

All male mice at 7 weeks of age were purchased from Hunan Silaike Jingda Laboratory Animal Co., Ltd. (specific pathogen-free [SPF]-grade, Hunan, China; license number SCXK2019-0004). After 7 days of adaptive feeding in SPF animal laboratory, forty-eight C57BL/6 mice were randomly divided into four groups: the control group (n = 12), ISO group (5 mg/kg, n = 12), ISO + Col 0.5 mg/kg group (Col-L group, n = 12) and ISO + Col 1.0 mg/kg group (Col-H group, n = 12). The 5 mg/kg/d of isoproterenol was subcutaneously injected for 14 days to induce the model of left ventricular remodeling and cardiac dysfunction. The control group was injected with equal volume of saline. Meanwhile, mice in the Col-L and Col-H groups were intragastrically administered with the colchicine of 0.5 mg/kg/d and 1.0 mg/kg/d for 14 days, respectively. And the control group and ISO groups were intragastrically administered the equal volume of double-distilled water. All animal experiments were performed in accordance with Animal Care and Use Guidelines of China and were approved by the Animal Use and Care Committee of Zunyi Medical University.

### Detection of the index of left ventricular function

After 14 days of administration, mice were anaesthetized. The index of left ventricular function such as Left Ventricular Ejection Fraction (LVEF), Left Ventricular Fractional Shortening (LVFS), Left Ventricular End-Diastole Volume (LVEDV) and Left Ventricular End-Systole Volume (LVESV) were measured using Vevo2100 system of small animal echocardiography imaging (Visual Sonics Corporation, Toronto, Canada).

### Measurement of the left ventricular mass index

After body weight was measured, mice were anaesthetized. The chest cavity of the mice was immediately opened. The left ventricle (including septum) was separated and weighed. Then the left ventricular mass index (LVMI) was calculated as follows: LVMI = the left ventricular weight (mg) / the body weight (g) × 100.

### H&E staining

The left ventricular myocardial tissues of mice were fixed in 4% formaldehyde solution for 48 h, dehydrated with the different concentrations of alcohol and embedded in paraffin. Then the sections were stained with H&E. Morphological changes of the left ventricle were observed under an optical microscope (BX-43; Olympus, Tokyo, Japan).

### Western blot analysis

50 mg of left ventricle myocardial tissue were mixed with 500 μl of RIPA lysate. The mixture was homogenized on ice for 30 min. Then the solutions were then centrifuged for 15 min at 12,000 r/min and 4 °C. The total protein concentration of the supernatant was determined by BCA (Generay, Shanghai, China, Cat no: GK5012). Protein extracts (30μg in 10 μl) were separated by electrophoresis using 10% sodium dodecyl sulfate-polyacrylamide gel and transferred to PVDF membranes and blocked with 8% non-fat milk for 3 h. Subsequently, the blots were incubated with antibodies against PPARα (1:1000, Proteintech, Wuhan, China, Cat no: 15540-1-AP), PGC-1α (1:5000, Proteintech, Cat no: 66369-1-Ig), CPT-1α (1:2000, Proteintech, Cat no: 15184-1-AP), MCAD (1:2000, Proteintech, Cat no: 55210-1-AP), and GAPDH (1:5000, Proteintech, Cat no: 10494-1-AP) at 4 °C for 18 h. Then the membranes were probed with secondary antibodies (1:5000, Affinity Biosciences, USA, Cat no: S0001) for 1 h at 4 °C. Finally, the ChemiDoc imaging system (BIO-RAD, CA, USA) was used to obtain images after ECL chemiluminescence (Tanon, USA, Cat no: 180-501). Then the Image Lab (BIO-RAD, CA, USA) was used to analyze the grey value of the protein band.

### Molecular docking

Molecular docking calculations were performed using Autodock 4.2.6 (La Jolla, CA, USA), and the affinity between Colchicine and PPARα was observed using Autodock Tools software. The three-dimensional (3D) protein structures of PPARα (PDB ID: 6I38) were retrieved from the Protein Data Bank. The molecular docking of the colchicine and PPARα binding sites was analyzed using Autodock software.

### Statistical analysis

Data were analyzed using one-way ANOVA with SPSS 18.0 software, and all the results are presented as the . Post hoc comparisons were performed using LSD with equal variances and with Dunnett's T3 with unequal variances, and $P < 0.05$ was considered statistically significant.

## Results

### Colchicine attenuated isoproterenol-induced CHF mice

The present study aimed to investigate the impact of colchicine on left ventricular function in isoproterenol-induced mice. Left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) were utilized as reliable indices to assess the systolic function of the left ventricle and to gauge its blood discharge capacity. In comparison to the control group, the mice in the isoproterenol-induced group exhibited a notable increase in left ventricular wall thickness and a significantly larger ventricular cavity (Fig. 1A). Moreover, LVEF and LVFS were significantly reduced ($P < 0.05$, Fig. 1B and Fig. 1C), with LVEF experiencing a substantial decrease of 35.95%. Additionally, left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were significantly elevated ($P < 0.05$, Fig. 1D and Fig. 1E) in the isoproterenol-induced group. However, in the Col-H group, there was a notable reduction in left ventricular wall thickness and a significant narrowing of the chamber (Figure 1A); Additionally, both LVEF and LVFS showed significant increases, with LVEF specifically increasing by 24.5% ($P < 0.05$, Figures 1B & 1C), Furthermore, LVEDV and LVESV exhibited significant decreases ($P < 0.05$, Figures 1D & 1E) when compared to the ISO group. These findings indicate that the administration of colchicine (1.0 mg/kg) can effectively enhance left ventricular function in mice.

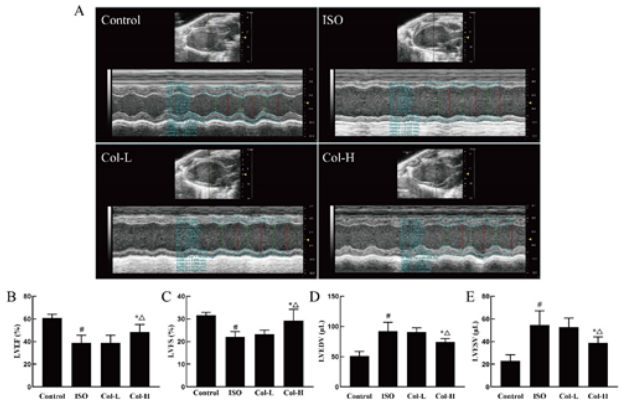


**Figure 1:** Effect of colchicine on left ventricular function in isoproterenol-induced mice. (A) Left ventricular ultrasound results, (B) LVEF, (C) LVFS, (D) LVEDV and (E) LVESV. ($\bar{x} \pm s$, n = 5) #$P < 0.05$ versus the control group; *$P < 0.05$ versus the ISO group; *$P < 0.05$ versus the Col-L group. Col: colchicine; ISO: isoproterenol; LVEF: left ventricular ejection fraction; LVFS: left ventricular fractional shortening; LVEDV: left ventricular end-diastole volume and LVESV: left ventricular end-systole volume.

Conversely, in the ISO group, the LVMI demonstrated a 26.25% increase compared to the control group ($P < 0.05$, Figure 2). However, the administration of colchicine (1.0 mg/kg) resulted in a 10.85% decrease in LVMI when compared to the ISO group ($P < 0.05$, Figure 2).

### Colchicine alleviated the morphological changes in mice with CHF

As depicted in figure 3, the histological analysis using H&E staining revealed that the left ventricle in the control group exhibited no detrimental alterations. Conversely, the ISO group displayed disorganized and irregular arrangement of myocardial cells, along with cardiomyocyte hypertrophy and infiltration of inflammatory cells. However, administration of colchicine (1.0 mg/kg) ameliorated myocardial hypertrophy and restored the orderly arrangement of myocardial cells, leading to a noticeable reduction in inflammatory cell infiltration.

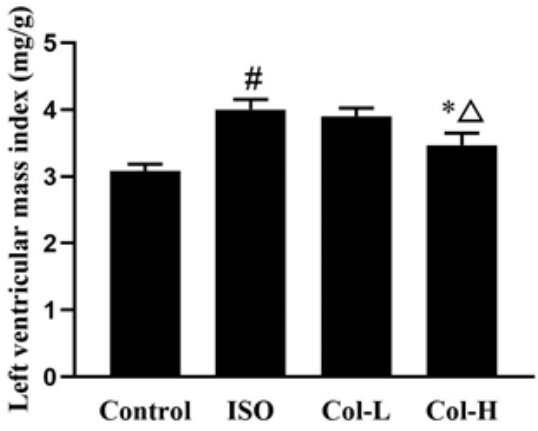


**Figure 2:** Effect of colchicine on left ventricular mass index in isoproterenol-induced mice. ($\bar{x} \pm s$, n = 10) #$P < 0.05$ versus the control group; *$P < 0.05$ versus the ISO group; *$P < 0.05$ versus the Col-L group. Col: colchicine; ISO: isoproterenol.

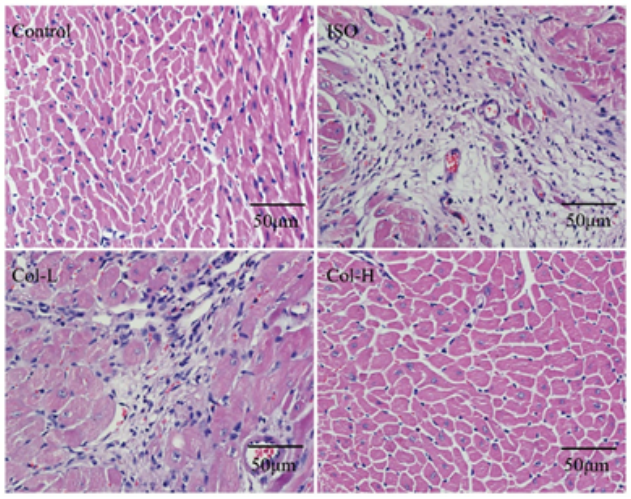


**Figure 3:** Effects of colchicine on the pathological changes of the left ventricle in isoproterenol-induced mice via H&E staining. Col: colchicine; ISO: isoproterenol.

### Effects of colchicine on the protein expressions of PGC-1α/PPARα in the left ventricle of isoproterenol-induced mice

It is worth noting that PGC-1α serves as a co-activator of PPARα. PPARα is essential regulators of myocardial energy metabolism. Therefore, further investigation is warranted to elucidate the potential mechanisms that may be involved in mediating the protective effects of colchicine, the study performed western blot to detect the protein expression of PGC-1α and PPARα. As showed in figure 4A, isoproterenol remarkably down-regulated PGC-1α protein expression by 54.37%, PPARα protein expression by 28.66%, compared to the control group (Figures 4A & B). However, the expression of PGC-1α and

PPARα protein was significantly up-regulated by 113.25% 49.66% and after treatment with 1.0 mg/kg colchicine ($P < 0.05$, Figures 4A & B). The results showed that colchicine (1.0 mg/kg) increased the protein levels of PGC-1α and PPARα in the left ventricle.

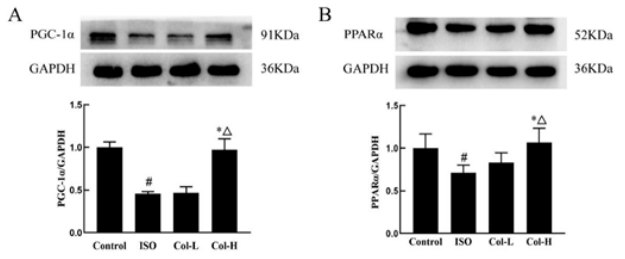


**Figure 4:** Effect of colchicine on the protein expressions of PPARα and PGC-1α in the left ventricle of isoproterenol-induced mice. (A) PPARα protein expression and (B) PGC-1α protein expression. ($\bar{x} \pm s$, n = 5) #P < 0.05 versus the control group; *P < 0.05 versus the ISO group; *P < 0.05 versus the Col-L group. Col: colchicine; ISO: isoproterenol; PPARα: peroxisome proliferator-activated receptor α; PGC-1α: peroxisome proliferator-activated receptor γ coactivator-1α.

Colchicine regulated the expression of CPT-1α and MCAD in the left ventricle of isoproterenol-induced mice CPT-1α converts fatty acyl-CoA into acylcarnitine. MCAD is key enzymes involved in fatty acid β-oxidation. As indicated in figure 5A, CPT-1α in the ISO group was decreased by 52.46% compared with that in the control group ($P < 0.05$, figure 5A). However, the protein level of CPT-1α was found to be elevated by 59.12% in the Col-H treatment groups compared with that in the ISO group ($P < 0.05$, figure 5A).

As indicated in Figure 5B, MCAD in the ISO group was decreased by 36.54% compared with that in the control group ($P < 0.05$, figure 5B). However, the protein level of MCAD was found to be elevated by 69.10% in the Col-H treatment groups compared with that in the ISO group ($P < 0.05$, figure 5B). The results showed that colchicine promoted the protein expressions of CPT-1α and MCAD in the left ventricle.

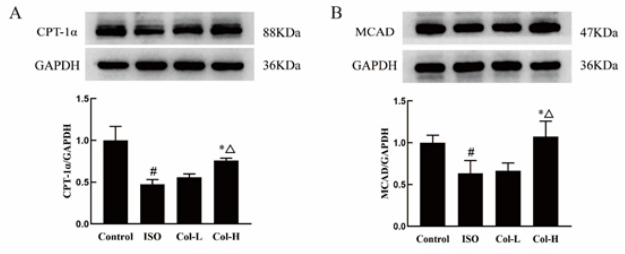


**Figure 5:** Effect of colchicine on the protein expressions of CPT-1α and MCAD in the left ventricle of isoproterenol-induced mice. (A) CPT-1α protein expression and (B) MCAD protein expression. ($\bar{x} \pm s$, n = 5) #P < 0.05 versus the control group; *P < 0.05 versus the ISO group; *P < 0.05 versus the Col-L group. Col: colchicine; ISO: isoproterenol; CPT-1α: carnitine palmitoyltransferase-1α; MCAD: medium-chain acyl-CoA dehydrogenase.

### Molecular docking of the colchicine and PPARα

Molecular docking analysis was applied to confirm whether colchicine binds to the PPARα proteins. It demonstrated that the binding energy of colchicine and PPARα were -7.06 kcal/mol; and colchicine directly bound to PPARα (Figure 6A). Colchicine is mainly bound in the hydrophobic cavity inside the PPARα protein (Figures 6B & C). Figure 6C showed that the O atoms in colchicine interact with Thr279, Thr283, Ala333 and Tyr334 in PPARα, respectively, which demonstrated the binding modes and interactions within the amino acid pocket. The results indicated that colchicine directly bound to PPARα.

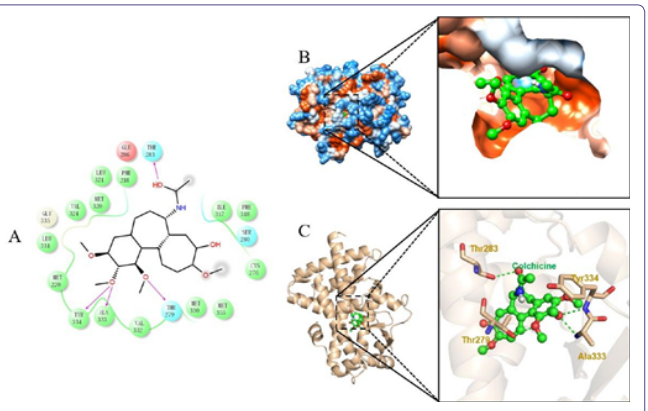


**Figure 6:** Molecular docking of the colchicine and PPARα. (A) Two-dimensional binding mode of colchicine to PPARα (B) A visual of the binding sites between colchicine and PPARα (C) The crystal structure of colchicine (green) displaying PPARα (yellow) bound to the docking pocket.

## Discussion

Congestive Heart Failure (CHF) is a condition characterized by myocardial damage resulting from a range of heart diseases, leading to structural and functional alterations in the heart. These changes ultimately impair the heart's ability to pump and fill effectively, culminating in an irreversible end stage [16]. Given the impact of CHF on various cardiovascular diseases, it is crucial to inhibit its occurrence and progression. Isoproterenol is currently acknowledged as a valuable tool for creating CHF models due to its simplicity and short duration [11,12]. The model has the advantages of the simple operation and the short cycle. The present study demonstrates that, it was showed that, in comparison to the control group, LVEDV and LVESV were significantly increased, and LVEF (38.93±6.01) was decreased by 35.95% in the ISO group. Meanwhile, LVMI also was increased in isoproterenol-induced mice evidently. Furthermore, H&E staining showed that the myocardial hypertrophy, and the infiltration of inflammatory cells were observed in isoproterenol-induced mice. All the aforementioned findings indicate that the administration of isoproterenol effectively induced the model of Congestive Heart Failure (CHF) in this particular study.

Colchicine, derived from the autumn crocus plant, was first purified by Geiger in 1833. Numerous studies have demonstrated that colchicine possesses the ability to protect cardiomyocytes in models of myocardial injury induced by Hypoxia/Reoxygenation or angiotensin II [17,18]. In the present investigation, the ultrasound results revealed that the administration of colchicine at a dosage of 1.0 mg/kg resulted in enhanced Left Ventricular Ejection Fraction (LVEF) and left ventricular fractional shortening (LVFS), as well as decreased Left Ventricular End-Diastolic Volume (LVEDV) and Left Ventricular End-Systolic Volume (LVESV). These findings suggest that colchicine at a dosage of 1.0 mg/kg effectively improves cardiac function and attenuates left ventricular remodeling in mice induced with isoproterenol.

The aberration in myocardial energy metabolism can contribute to the onset and progression of Congestive Heart Failure (CHF). As the myocardium undergoes differentiation and maturation, lipid metabolism becomes the primary energy source [19]. Most notably, with the occurrence of CHF, myocardial metabolism predominantly shifts towards glucose utilization instead of lipid metabolism [20]. This shift is unable to sustain the heart's energy requirements over an extended period, ultimately resulting in the disruption of myocardial energy metabolism [21].

PGC-1α serves as an activator of PPARα, which plays a regulatory role in fatty acid β-oxidation. PGC-1α binds with PPARα and then PPARα is activated to up-regulate the expression of CPT-1α and MCAD, which promotes the β-oxidation of fatty acids and improves myocardial energy metabolism [22,23]. Gao et al. have found t a decrease in the expression of PGC-1α in left heart tissue of rats with heart failure induced by acute myocardial infarction, resulting in inhibited fatty acid β-oxidation [24]. Hereby, we further explored the protein expression of PGC-1α of left ventricular tissue in mice in the present study. We found that colchicine (1.0 mg/kg) administration inhibited the decreased protein expression of PGC-1α of left ventricular tissue induced by isoproterenol in mice. PPARα is the key transcriptional factor of fatty acid β-oxidation [6,7]. Studies have shown that fatty acid oxidation rates were reduced significantly in hearts of PPARα knockout mice compared with WT mice [25,26]. Gélinas et al. found that the expression of CPT-1α of the myocardial tissue was down-regulated in PPARα knockout mice, and the β-oxidation of fatty acids was reduced significantly [27]. Chen et al., also have found that the expression of PPARα was decreased and then fatty acid β-oxidation was inhibited s in a heart failure mice model induced by myocardial infarction [28]. In the present study, we found that colchicine (1.0 mg/kg) administration elevated the decreased protein expression of PPARα of left ventricle induced by isoproterenol in mice.

PPARα has been found to have a promoting effect on the expression of CPT-1α and MCAD in heart tissue [29]. Specifically, CPT-1α is localized in the outer mitochondrial membrane and facilitates the conversion of fatty acyl-CoA into acylcarnitine through carnitine translocase, enabling its transportation to the inner mitochondrial membrane for subsequent fatty acid β-oxidation. MCAD is responsible for promoting the β-oxidation of medium-chain fatty acids [30]. Consequently, in this study, we employed western blotting to further investigate the alterations in CPT-1α and MCAD levels in left ventricular tissue. As expected, colchicine (1.0 mg/kg) administration evidently elevated the decreased protein expressions of CPT-1α and MCAD of left ventricular tissue induced by isoproterenol in mice. It demonstrated that colchicine (1.0 mg/kg) improved CHF through up-regulating the PGC-1α/PPARα signaling pathway and then to promote myocardial fatty acid β-oxidation.

The present study utilized AutodockTools molecular docking software analysis to investigate the binding of colchicine to the PPARα protein. The results indicated a binding energy of -7.06 kcal/mol between colchicine and PPARα. Furthermore, the interaction between the O atoms in colchicine and Thr279, Thr283, Ala333, and Tyr334 in PPARα suggested the binding of colchicine to the PPARα protein.

Overall, colchicine was found to alleviate cardiac dysfunction induced by isoproterenol in mice, potentially through the up-regulation of PGC-1α, PPARα, CPT-1α, and MCAD and then to promote myocardial fatty acid β-oxidation, thereby promoting a mechanism of action (Figure 7).

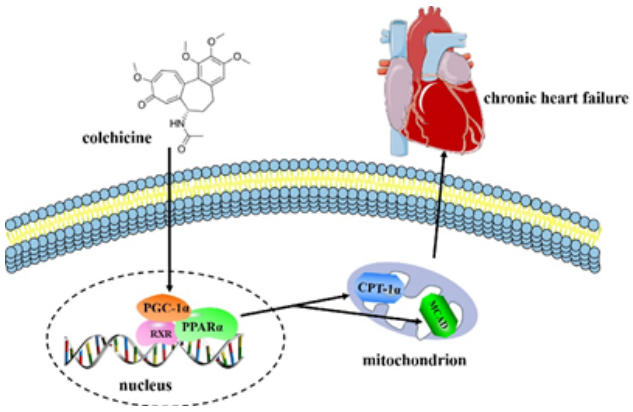


**Figure 7:** A schematic showing the underlying mechanisms of the cardioprotective effect effects of colchicine in isoproterenol-induced mice.

## Conclusion

In conclusion, colchicine exhibits a therapeutic potential in ameliorating cardiac dysfunction in isoproterenol-induced mice, potentially mediated, at least in part, by enhancing the activity of PGC-1α, PPARα, CPT-1α, and MCAD and to enhance the fatty acid β-oxidation.

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