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*Original Article*

# Morin, a plant derived flavonoid, modulates the expression of peroxisome proliferator-activated receptor-γ coactivator-1α mediated by AMPK pathway in hepatic stellate cells

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**Abstract:** Morin exerts inhibitory effects on hepatic stellate cell (HSC) stimulation which is considered important step for fibrogenesis in liver. These morin-induced inhibitory effects are mediated through enhancement in the expression levels of peroxisome proliferator-activated receptor-γ (PPARγ). PPARγ plays a critical role in inhibition of HSC stimulation. Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) acts as a co-activator for PPARγ. Hence, studies directed at examining the influence of morin on PGC-1α may help to understand the mechanisms behind the morin induced suppression of HSC stimulation and liver fibrosis via PPARγ. The current research was therefore designed to examine the effect of morin on the expression levels of PGC-1α in HSCs under *in vitro* conditions and to attempt to investigate the involved potential mechanisms by western blotting, RT-PCR, and transfection assays. The results revealed that morin increased the expression of PGC-1α and the effects of morin on the expression of PGC-1α were positively associated with the stimulation of adenosine monophosphate-activated protein kinase (AMPK). Additionally, morin enhanced superoxide dimutase-2 (SOD-2) transcript levels as well as the activity via AMPK/PGC-1α axis. Furthermore, PGC-1α was found to suppress α1 (I) collagen transcript levels in HSCs. Taken together, these results revealed that the effect of morin on the enhancement of the expression of PGC-1α is mediated through AMPK pathway which ultimately leads to increase in the activity of PPARγ and SOD-2.

**Keywords:** Morin, hepatic stellate cell, fibrogenesis, peroxisomes

## Introduction

Hepatic stellate cell (HSC) is one of the appropriate cell types for growth of liver fibrosis. HSC initiation is considered as one of the important phases in liver fibrogenesis. HSC initiation is comparable to the adipocyte to pre-adipocyte trans-differentiation [1]. There are concrete evidences in literature that the adipocyte transcription factors, like peroxisome proliferator-activated receptor-γ (PPARγ) and PPARα, exhibit anti-fibrotic activity [2]. PPARγ and PPARα have been reported to be linked with the advancement of adipocyte differentiation [3]. Additionally, it has been observed that PPARγ plays an important role in regulating the transcription of HSC stimulation [4]. Transcription factors exercise their influence by linking with co-activators or co-repressors. Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is a PGC-1 family member which has long been reported to be involved in controlling the cellular carbohydrate and lipid metabolism [5]. Moreover it has also been reported to play a vital part in cell fate decision of adipocyte [6]. PGC-1α can co-activate several nuclear receptors and non-nuclear receptor transcription factor targets [7]. Antioxidant flavonoids have received considerable attention in the recent past as a remedy for the treatment of several diseases and disorders. There are evidences that about the inhibitory effects of flavonoids on liver [8]. Consistently, flavonoids have been shown to increase PPARγ expression in different cell types [9] as well as exhibit the capacity to modulate HSC cell growth and expres-

sion of extracellular matrix through enhancement of PPARγ expression [10]. Morin, a natural flavonoid isolated from several plants belonging to the family *moriaceae,* has been reported to exhibit tremendous pharmacological potential. In particular it has been reported to induce mitochondrial-dependent apoptosis in cancerous cells. Herein the present study we studied the effect of morin *in vitro* on the PGC-1α expression, PPARγ and HSCs. Moreover, the signaling cascade facilitating the influence of morin on PGC-1α was also studied.

## Materials and methods

### *Materials*

Morin and other all chemicals and regents used in the present study were purchased from Sigma (St. Louis, MO, USA).

### *Isolation of HSC and culturing*

Sprague-Dawley rats were used for isolation of HSCs as reported previously [11]. For culturing, isolated HSCs were seeded in 25 $cm^2$ plastic flasks. Prior to morin administration, HSCs were shifted to the fresh flasks ($2 \times 10^6$/flask) or 12-well plates ($4 \times 10^5$/w) or 6-well plates ($1 \times 10^6$/w). The cells were then administrated with morin (in DMSO), AICAR, Compound C, or the solvent in DMEM medium with 2% FBS. The Institutional ethical committee provided the approval for carrying out the experiments.

### *Western blot analysis*

After administration with various concentrations of ME, RB355 cells were harvested and lysed in lysis buffer. Out of the total protien samples 20 μg aliquot was separated on SDS-PAGE gel (10%). The gel was then transferred to nitrocellulose membranes, blocked with 6% BSA and probed with a primary antibody. This was followed by probing with the required secondary antibody. Finally, the signal was perceived with WEST-SVE Up™ lumina-based ECL reagent (ABrontier, Korea). Proteins were revealed by primary antibodies and successively by horseradish peroxidase-conjugated secondary antibodies.

### *RNA isolation, cDNA synthesis and real-time PCR*

Total RNA was extracted by using RNeasy RNA isolation kit (Qiagen) and the whole procedure was carried out in accordance with the manufacturer's protocol. Thereafter, cDNA was synthesized with the help of RevertAid cDNA synthesis kit (Fermentas) strictly in accordance with the manufacturer's protocol. To carry out the RT-PCR, the cDNA was diluted (20 times) and quantitative RT-PCR was carried out in three replicates in ABI StepOne Real time (Applied biosystems) using SYBR Green Master Mix (Fermentas). The quantitative variation was examined by the relative quantification method ($\Delta\Delta^{-CT}$) and actin was used as reference to normalize the data.

### *Transient transfection assays*

The PPARγ activity reporter plasmid pPPREX3-TK-Luc harbors 3 consensus PPARγ-responsive elements and a Photinus luciferase vector. Plasmid pSV-PGC-1α codes for WT mouse PGC-1α.

Plasmid pGL3 PGC-1α-Luc contains mouse PGC-1α promoter. The plasmids were procured from Addgene Inc, (Cambridge, MA, USA). Plasmid pwtAMPK$\alpha_2$ and plasmid pdn AMPK$\alpha_2$ code for WT AMPK$\alpha_2$ and dominant-negative AMPK$\alpha_2$ respectively.

HSCs in 12-well plates or 6-well plates were transfected with the corresponding plasmid transiently by Lipofect AMINE reagent by following the manufacturer's protocol. As the cells were transfected with pPPREX3-TK-Lucor pGL3 PGC-1α-Luc-(1.6 or 0.8 μg/well), 30 ng of Control vector expressing Renilla luciferase was taken to control the transfection efficiency. Data were normalized to pRL-TK activity.

### *SOD-2 activity*

For SOD-2 activity the cells were pre-washed with ice cold PBS, suspended and centrifuged at 1000 g. Cells were then suspended in HEPES buffer having EGTA, mannitol, and sucrose and homogenized. The lysate was then again subjected to centrifugation. SOD2 activity was finally determined by the SOD Assay Kit following manufactures protocol.

### *Statistical analysis*

Each experiment was carried out in three biological replicates. Statistical analysis was carried by One way ANOVA followed by Tukey's

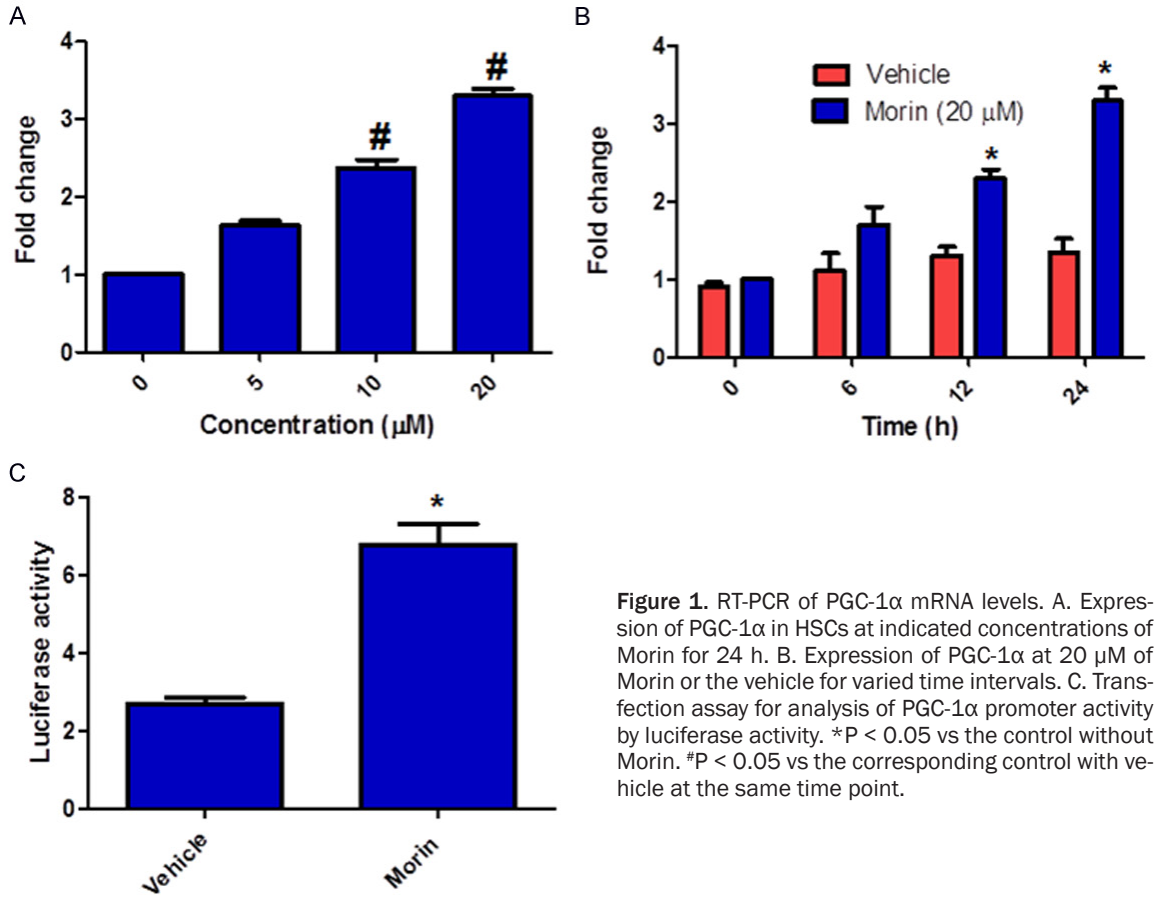


**Figure 1.** RT-PCR of PGC-1α mRNA levels. A. Expression of PGC-1α in HSCs at indicated concentrations of Morin for 24 h. B. Expression of PGC-1α at 20 μM of Morin or the vehicle for varied time intervals. C. Transfection assay for analysis of PGC-1α promoter activity by luciferase activity. *P < 0.05 vs the control without Morin. #P < 0.05 vs the corresponding control with vehicle at the same time point.

post hoc test by GraphPad prism 7 and the values were considered significant at $p < 0.05$.

## Results

*Morin enhances the expression of PGC-1α*

To investigate the effect of morin on the expression levels of PGC-1α, HSCs were administrated with various doses of morin for 24 h. The transcript levels of PGC-1α were estimated by RT-PCR (**Figure 1A**). It was observed that morin significantly enhanced the mRNA levels of PGC-1α dose dependently. 20 μM of morin caused 2.1-fold enhancement in the mRNA levels of PGC-1α in comparison to the untreated control. In order to further confirm the role of morin in enhancing the expression of PGC-1α expression, HSCs were administrated with 20 μM of morin for varied time intervals. The results of RT-PCR (**Figure 1B**) revealed that PGC-1α mRNA levels were upregulated at 12 h and the enhancement remained upto 24 h at least. Moreover, HSCs were transfected with pGL3 PGC-1α-Luc and treated with 20 μM of morin or the vehicle for a time period of 24 h (**Figure 1C**). The results of luciferase assay indicated that morin stimulated PGC-1α promoter activity. Taken together, these results indicate that morin increased PGC-1α transcription in cultured HSCs.

*Effect of morin on PGC-1α expression is mediated by AMPK activation*

As AMPK has been reported to play an important role in PGC-1α expression in skeletal muscle [12] and that morin increases the expression of PGC-1α in HSCs (**Figure 1**), the influence of 20 μM of morin on AMPK stimulation was investigated in HSCs.

The results of western blotting revealed that morin markedly enhanced the protein expression of p-AMPK at 60 min time interval (**Figure 2A**). Grounded on these observations, the effect of AMPK stimulation on the expression levels of PGC-1α was investigated. For this AICAR (AMPK activator) was administrated to HSCs or 20 μM of morin for 24 h. The transcript and pro-

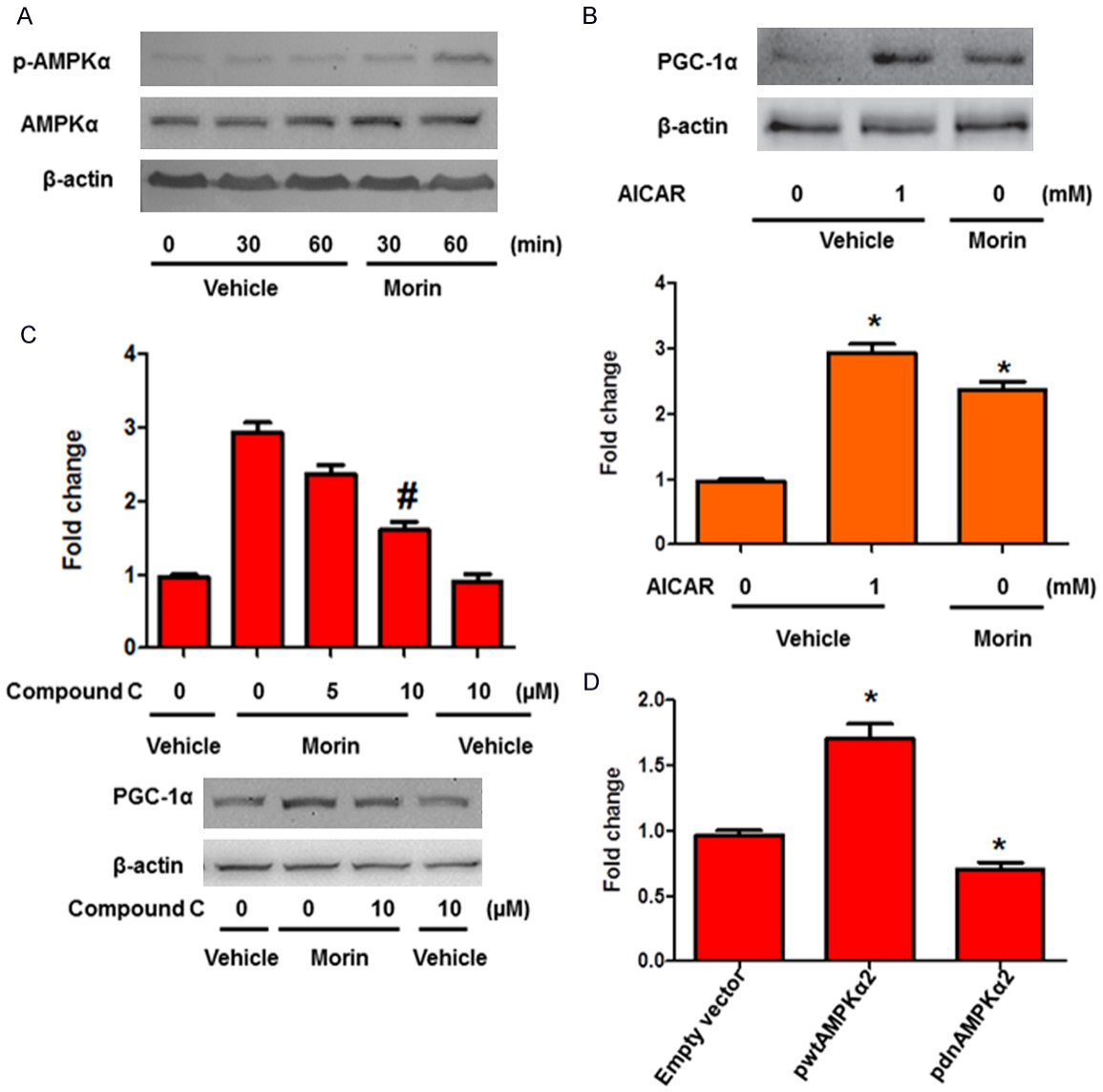


**Figure 2.** AMPK stimulation mediates the promotion effect of morin on the expression of PGC-1α in cultured HSCs. (A) Western blotting of phospho-AMPKα (Thr172) and AMPKα (n ¼3). (B) HSCs were treated with AICAR or 20 μM of morin or the vehicle for 24 h (C) HSCs were treated with Compound C (the specific AMPK inhibitor) for 30 min before incubation with 20 μM of morin or the vehicle for an additional 24 h and subjected to RT-PCR and western blotting. *P < 0.05 vs the control with vehicle. #P < 0.05 vs the control with morin alone or vs the control with Compound C plus vehicle (the first column on the right). (D) RT-PCR analyses of PGC-1α mRNA level. *P < 0.05 vs the control with empty vector.

tein expression levels of PGC-1α were examined (**Figure 2B**). The results indicated that AICAR and morin enhanced both the transcript as well as the protien expression levels of PGC-1α. 1 mM of AICAR was observed to enhance the mRNA levels of PGC-1α by 100% in comparison to the control. Further to validate the involvement of morin-triggered AMPK stimulation in promoting PGC-1α transcription, HSCs were pre-administrated with varied concentrations of Compound C (AMPK inhibitor) for 30 min prior to treatment with or without 20 μM of morin for 24 h more and thereafter the transcript and protein levels of PGC-1α were determined (**Figure 2C**). The results indicated that morin-induced enhancements in the mRNA and protein expression of PGC-1α are in part stabilized by Compound C. Additionally; HSCs were also transfected with pwtAMPK$\alpha_2$ or plasmid pdnAMPK$\alpha_2$ and treated with morin. The

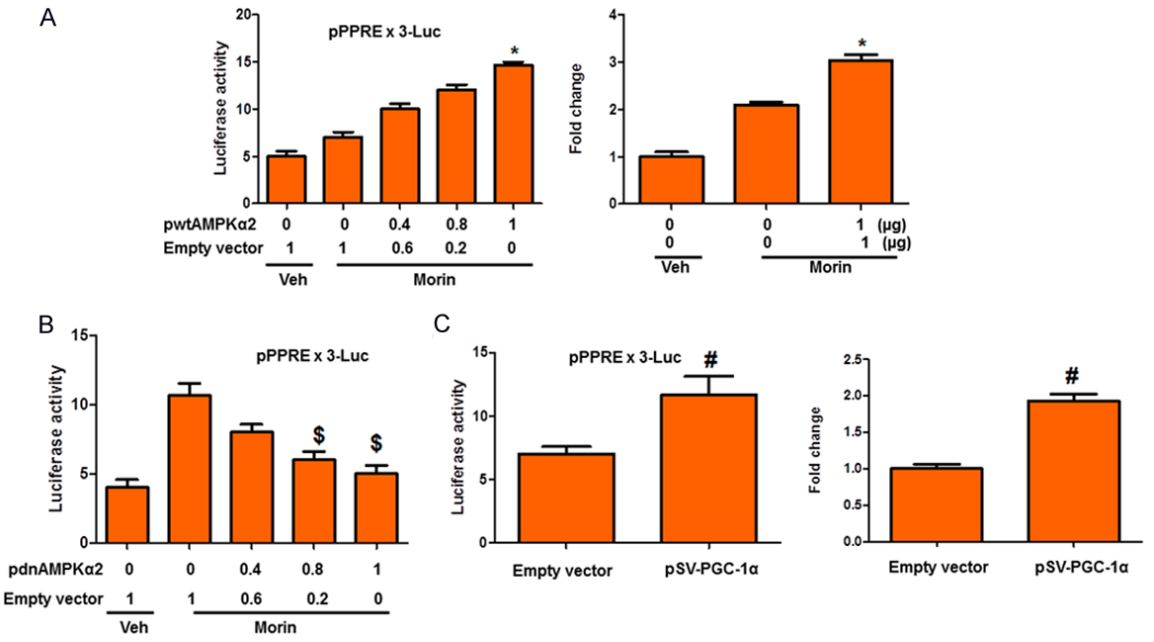


**Figure 3.** (A) HSCs transiently co-transfected with pPPRE 3-TK-Luc (0.8 μg/well) plus different doses of pwtAMPKα$_2$ and empty vector or transfected with pwtAMPKα$_2$ or empty vector before treatment with 20 μM of morin or the vehicle (Veh) for 24 h, (B) HSCs were co-transfected with pPPRE 3-TK-Luc (0.8 μg/well) plus different doses of pdnAMPKα$_2$ and empty vector before treatment 15 mM of morin or the vehicle (Veh) for 24 h, (C) or HSCs were administrated with morin transfected with pPPRE 3-TK-Luc (0.8 μg/well) plus pSV-PGC-1α (0.8 μg/well) or control empty vector for 24 h or transfected with pSV-PGC-1α or control empty vector for 24 h. The luciferase assay was performed or LXRα and mRNA levels relative to cyclophilin were examined by real-time PCR. *P < 0.05 vs the cells with morin and without pwtAMPKα. *P < 0.05 vs the cells with morin and without #P < 0.05 vs the cells with empty vector.

RT-PCR results revealed that pwtAMPKα$_2$ enhanced the mRNA levels of PGC-1α while as pdnAMPKα$_2$ decreased the mRNA levels of PGC-1α in comparison to the control (**Figure 2D**). Taken together, these outcomes indicate that AMPK stimulation is requirement for the morin induced expression of PGC-1α in HSCs.

*Involvement of PGC-1α in morin-induced transactivation activity of PPARγ and enhancement of mRNA levels of LXRα*

Morin-induced stimulation of AMPK caused enhanced expression of PGC-1α in HSCs (**Figure 2**) and PGC-1α causes co-activation of PPARγ trans-activation activity [13]. Hence, the influence of morin-triggered stimulation of AMPK on trans-activation activity of PPARγ and levels of mRNA of LXRα (a PPARγ target gene), were also studied. HSCs were co-transfected transiently with pPPRE-TK-Luc (for determination of trans-activation activity of PPARγ) plus pwtAMPKα$_2$ (coding for rat wild type AMPKα$_2$) prior to incubation with morin or HSCs were transfected with or without pwtAMPKα$_2$ prior to incubation with morin (**Figure 3A**) or HSCs were co-transfected transiently with pPPRE-TK-Luc plus pdnAMPKα$_2$ (encoding rat dominant negative AMPKα$_2$) prior to incubation with morin (**Figure 3B**). The results of luciferase assay revealed that pwtAMPKα$_2$ increased and pdnAMPKα$_2$ suppressed the morin-induced PPARγ trans-activation activity (**Figure 3A**, **3B**), indicating that morin-induced stimulation of AMPK enhanced the PPARγ trans-activation in HSCs. The results of RT-PCR revealed that pwtAMPKα$_2$ also increased morin-induced LXRα expression (**Figure 3A**), supporting the influence of morin-triggered stimulation of AMPK on PPARγ activity. Additionally, HSCs were co-transfected transiently with pPPRE-TK-Luc plus pSV-PGC-1α or the empty vector or HSCs were transfected with pSV-PC-1α or control empty vector (**Figure 3C**). The results indicated that that overexpression of PGC-1α enhances luciferase activity and LXRα mRNA levels, demonstrating the role of PC-1α in the promotion of trans-activation activity of mRNA levels of PPARγ and LXRα in HSCs. As morin-triggered stimulation of AMPK caused induc-

tion of expression of PC-1α in HSCs (**Figure 2**), the outcomes of **Figure 3** imply that PGC-1α was associated with morin-triggered trans-activation activity of PPARγ in HSCs.

*Morin enhances activity and expression of SOD2 via AMP/PGC-1α axis and PGC-1α inhibits its expression of α1 (I) collagen*

Accretion of significant amounts of ROS has been reported in injured liver which ultimately causes fibrosis by stimulating HSCs [14]. To scavenge ROS the antioxidant enzymes in mitochondria such as SOD-2 form the first line of defense. It has further been reported that PGC-1α enhances the expression of SOD-2 and lessens the accumulation of ROS in vascular endothelial cells [15]. Hence, we examined the influence of PGC-1α on the transcript levels and activity of SOD-2 in HSCs.

Afterward HSCs were transfected with pSV-PGC-1α or the empty vector and treated with morin and the expression levels and activity of SOD-2 were investigated (**Figure 4**). The results indicated that PGC-1α overexpression or morin administration considerably enhanced the expression levels and activity of SOD2 which could be enhanced by PGC-1α plus morin. Consistent with the influence of morin on expression of PGC-1α via AMPK pathway, we investigated the effects of morin and AMPK pathway on the mRNA levels and activity of SOD-2. For this, HSCs were administrated with morin, AICAR, or morin plus Compound C (**Figure 4B**). The results revealed that both morin and AICAR enhanced the expression and activity of SOD-2 and at the same time Compound C lessened the effect of morin on the expression and activity of SOD-2. Together with the enhancing effect of PGC-1α on transcription and activity of SOD-2 (**Figure 4A**) and the outcomes that AMPK activation mediates the effect of morin on the expression of PGC-1α (**Figure 2**), the results in **Figure 4B** imply that morin enhanced the expression and activity of SOD-2 via AMPK/PGC-1α axis.

PGC-1α enhanced the expression of SOD-2 (**Figure 4A**) and acts as PPARγ co-activator. Additionally, SOD and PPARγ both inhibit expression of α1 (I) collagen (a major component of ECM) in HSCs [16]. Therefore, HSCs were transfected with pSV-PGC-1α or the empty vector, treated with morin and the expression of α1 (I) collagen was investigated. RT-PCR analysis (**Figure 4C**) revealed that PGC-1α overexpression or incubation with morin reduced the expression of α1 (I) collagen which could be significantly suppressed by PGC-1α plus morin treatment.

## Discussion

HSC stimulation is an important step in liver fibrogenesis as the stimulated HSCs lead to the production of ECM. The results of the current study revealed that that morin enhanced the PGC-1α expression, which acts as a PPARγ co-activator in HSCs under *in vitro* conditions. The mechanistic studies revealed that morin-triggered AMPK stimulation promoted the effect of morin on the expression of PGC-1α. Additionally, morin stimulates the expression of SOD-2 via AMPK/PGC-1α axis and PGC-1α was found to suppress the transcription of α1 (I) collagen, a principal constituent of ECM in HSCs.

PPARγ has a vital role in the inhibition of HSC stimulation and has been considered as a prospective target for suppression of HSC stimulation [17]. The results revealed the enhancing effect of morin on expression of PGC-1α which acts as a co-activator for PPARγ in HSCs under *in vitro* conditions. Given the results of the study, it appeared rational that besides the effect of morin on activity of PPARγ via enhancement of the expression of PPARγ [18], morin might also lead to activation of PPARγ through enhancement of PGC-1α in HSCs and hence influences HSCs. It has been reported that AMPK stimulation negatively controls the expression of α1 (I) collagen in HSCs [19] as well as mouse HSCs [20] Consistent with this, the results of the present study revealed that that morin-triggered AMPK stimulation enhanced PGC-1α expression and PGC-1α in turn decreased the expression of α1 (I) collagen, indicating that PGC-1α might arbitrate the influence of AMPK stimulation on the expression of α1 (I) collagen in HSCs *in vitro.*

There are concrete evidences in literature that substantial amounts of ROS are accumulated in injured liver which adds to liver fibrosis through activation of HSCs [21]. Moreover, it has also been reported that antioxidants can inhibit the HSC stimulation [22]. Antioxidant enzymes and other non enzymic molecules

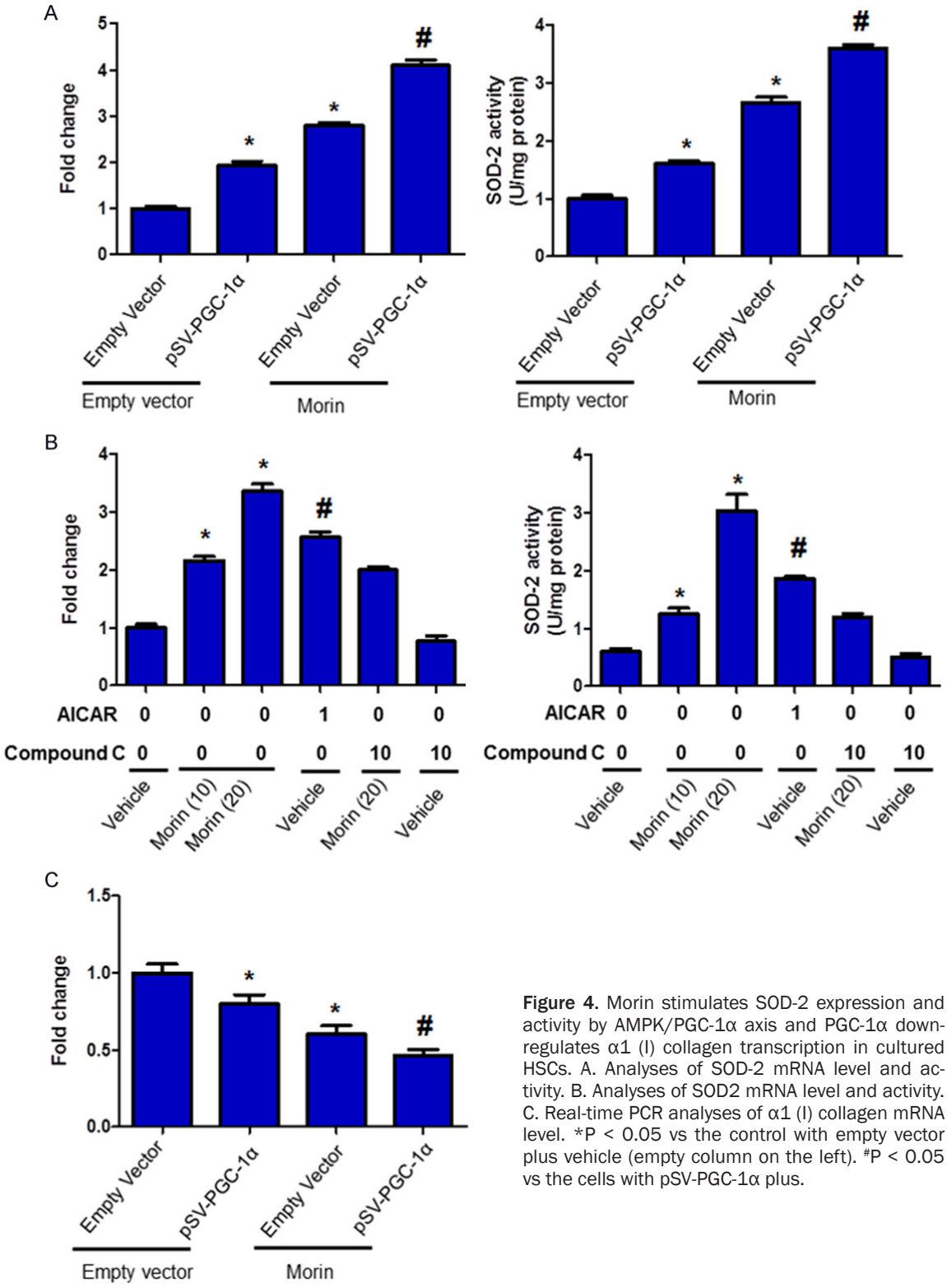


**Figure 4.** Morin stimulates SOD-2 expression and activity by AMPK/PGC-1α axis and PGC-1α down-regulates α1 (I) collagen transcription in cultured HSCs. A. Analyses of SOD-2 mRNA level and activity. B. Analyses of SOD2 mRNA level and activity. C. Real-time PCR analyses of α1 (I) collagen mRNA level. *P < 0.05 vs the control with empty vector plus vehicle (empty column on the left). #P < 0.05 vs the cells with pSV-PGC-1α plus.

scavenge ROS in cells and flavonoids such as morin are potent antioxidant [23] and inhibit HSC stimulation through induction of glutathione synthesis [24] which exhibits the capacity to scavenge ROS or alternatively acts a cofactor for several antioxidant enzymes. In the pres-

ent study, morin was found to enhance the expression and activity of SOD-2, and morin-triggered AMPK/PGC-1α axis may account for the effect of morin on SOD-2 in HSCs.

Therefore, these results indicated that antioxidant potential of morin may be facilitated, by SOD-2 in HSCs and suggests a new mechanism behind the effect of morin on HSCs. However, these results do not eliminate the involvement of other antioxidant enzymes in morin-induced PGC-1α. Moreover, the results of the present study revealed the negative influence of PGC-1α on the expression of α1 (I) collagen, a principal constituent of ECM in HSCs.

## Conclusion

In conclusion, we proposed that morin can enhance the expression of PGC-1α through stimulation of AMPK. Morin-induced PGC-1α activates PPARγ and increases expression of SOD-2 in HSCs which in turn exerts an inhibitory effect on the expression of α1 (I) collagen. These results indicate a new prospective account for the suppressing effect of morin on liver fibrogenesis.

## Disclosure of conflict of interest

None.

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## References

[1] Caligiuri A, Bertolani C, Guerra CT, Aleffi S, Galastri S, Trappoliere M, Vizzutti F, Gelmini S, Laffi G, Pinzani M, Marra F. Adenosine monophosphate-activated protein kinase modulates the activated phenotype of hepatic stellate cells. Hepatology 2008; 47: 668-676.

[2] Casini A, Ceni E, Salzano R, Biondi P, Parola M, Galli A, Foschi M, Caligiuri A, Pinzani M, Surrenti C. Neutrophil-derived superoxide anion induces lipid peroxidation and stimulates collagen synthesis in human hepatic stellate cells: role of nitric oxide. Hepatology 1997; 25: 361-367.

[3] Fu Y, Zheng S, Lin J, Ryerse J, Chen A. Curcumin protects the rat liver from CCl4-caused injury and fibrogenesis by attenuating oxidative stress and suppressing inflammation. Mol Pharmacol 2008; 73: 399-409.

[4] Galli A, Crabb DW, Ceni E, Salzano R, Mello T, Svegliati-Baroni G, Ridolfi F, Trozzi L, Surrenti C, Casini A. Antidiabetic thiazolidinediones inhibit collagen synthesis and hepatic stellate cell activation in vivo and in vitro. Gastroenterology 2002; 122: 1924-1940.

[5] Kawada T. Activation of peroxisome proliferator-activated receptor-α stimulates both differentiation and fatty acid oxidation in adipocytes. J Lipid Res 2011; 52: 873-884.

[6] Hazra S, Xiong S, Wang J, Rippe RA, Krishna V, Chatterjee K, Tsukamoto H. Peroxisome proliferator-activated receptor γ induces a phenotypic switch from activated to quiescent hepatic stellate cells. J Biol Chem 2004; 279: 11392-11401.

[7] Houglum K, Venkataramani A, Lyche K, Chojkier M. A pilot study of the effects of d-alpha-tocopherol on hepatic stellate cell activation in chronic hepatitis C. Gastroenterology 1997; 113: 1069-1073.

[8] Ip E, Farrell G, Hall P, Robertson G, Leclercq I. Administration of the potent PPARα agonist, Wy-14,643, reverses nutritional fibrosis and steatohe-patitis in mice. Hepatology 2004; 39: 1286-1296.

[9] Kawada N, Seki S, Inoue M, Kuroki T. Effect of antioxidants, resveratrol, quercetin, and N-acetylcysteine, on the functions of cultured rat hepatic stellate cells and Kupffer cells. Hepatology 1998; 27: 1265-1274.

[10] Giridharan VV, Soetikno V, Kodama M, Aizawa Y. Telmisartan att-enuates oxidative stress and renal fibrosis in streptozotocin induced diabetic mice with the alteration of angiotensin-(1-7) mas receptor expression associated with its PPAR-γ agonist action. Free Radic Res 2011; 45: 575-584.

[11] Liang H, Ward WF. PGC-1α: a key regulator of energy metabolism. Adv Physiol Educ 2006; 30: 145-151.

[12] Lowell BB. PPARγ: an essential regulator of adipogenesis and modulator of fat cell function. Cell 1999; 99: 239-242.

[13] Lu Z, Xu X, Hu X, Fassett J, Zhu G, Tao Y, Li J, Huang Y, Zhang P, Zhao B, Chen Y. PGC-1 alpha regulates expression of myocardial mitochondrial antioxidants and myocardial oxidative stress after chronic systolic overload. Antioxid Redox Signal 2010; 13: 1011-1022.

[14] O'Connell MA, Rushworth SA. Curcumin: potential for hepatic fibrosis therapy? Br J Pharmacol 2008; 153: 403-405.

[15] Qiu J, Zhou Q, Zhai X, Jia X, Zhou Y. Curcumin regulates delta-like homolog 1 expression in activated hepatic stellate cell. Eur J Pharmacol 2014; 728: 9-15.

[16] Ruby AJ, Kuttan G, Babu KD, Rajasekharan KN, Kuttan R. Anti-tumour and antioxidant activity of natural curcuminoids. Cancer Lett 1995; 94: 79-83.
[17] She H, Xiong S, Hazra S, Tsukamoto H. Adipogenic transcriptional regulation of hepatic stellate cells. J Biol Chem 2005; 280: 4959-4967.
[18] Shishodia S, Sethi G, Aggarwal BB. Curcumin: getting back to the roots. Ann N Y Acad Sci 2005; 1056: 206-217.
[19] Svegliati Baroni G, D'Ambrosio L, Ferretti G, Casini A, Di Sario A, Salzano R, Ridolfi F, Saccomanno S, Jezequel AM, Benedetti A. Fibrogenic effect of oxidative stress on rat hepatic stellate cells. Hepatology 1998; 27: 720-726.
[20] Tsukamoto H. Adipogenic phenotype of hepatic stellate cells. Alcohol Clin Exp Res 2005; 29: 132S-133S.
[21] Valle I, Alvarez-Barrientos A, Arza E, Lamas S, Monsalve M. PGC-1α regulates the mitochondrial antioxidant defense system in vascular endothelial cells. Cardiovasc Res 2005; 66: 562-573.
[22] Velayudham A, Dolganiuc A, Ellis M, Petrasek J, Kodys K, Mandrekar P, Szabo G. VSL#3 probiotic treatment attenuates fibrosis without changes in steatohepatitis in a diet-induced nonalcoholic steatohepatitis model in mice. Hepatology 2009; 49: 989-997.
[23] Xu J, Fu Y, Chen A. Activation of peroxisome proliferator-activated receptor-γ contributes to the inhibitory effects of curcumin on rat hepatic stellate cell growth. Am J Physiol Gastrointest Liver Physiol 2003; 285; G20-30.
[24] Zheng S, Chen A. Activation of PPARγ is required for curcumin to induce apoptosis and to inhibit the expression of extracellular matrix genes in hepatic stellate cells in vitro. Biochem J 2004; 384: 149-157.