**Ind. J. Pharm. Edu. Res., 2026; 60(4):1523-1531.**
https://www.ijper.org

Original Article

# Effect of Curcumin on High Glucose-Induced Oxidative Damage of Human Retinal Pigment Epithelial Cells through Regulation of AMPK/SIRT1 Pathway

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## ABSTRACT

**Objectives:** For investigating the impact of curcumin on High Glucose (HG)-evoked oxidative damage of human RPE cells (ARPE-19) and AMPK/SIRT1 pathway. **Materials and Methods:** CCK8 method was applied to measure ARPE-19 cell activity after curcumin treatment. Then, ARPE-19 cells were separated into control group (5 mmol/L glucose), HG group (30 mmol/L glucose), curcumin (20, 40, or 80 μmol/L)+HG groups and 80 μmol/L curcumin+HG+5 μmol/L AMPK inhibitor group. Flow cytometry was used for measuring the apoptosis of ARPE-19 cells and DCFH-DA probe loading method was applied to measure intracellular ROS level. ELISA was applied to measure the levels of SOD, GSH, MDA and LDH. Western blot was applied to measure the ARPE-19 cell apoptosis and AMPK/SIRT1 pathway related protein expression. **Results:** Different doses of curcumin (20, 40 and 80 μmol/L) had no effect on ARPE-19 cell viability versus control group. Comparison of control and HG groups, HG group had higher apoptosis rate, LDH release rate, ROS, MDA, Caspase-3 and Bax levels and lower GSH, SOD, Bcl-2, p-AMPK/AMPK, SIRT1 and PGC-1α levels. Compared to HG group, co-treatment of HG with 20, 40, or 80 μmol/L curcumin had lower apoptosis rate, LDH release rate, ROS, MDA, Caspase-3 and Bax levels and higher GSH, SOD, Bcl-2, p-AMPK/AMPK, SIRT1 and PGC-1α levels dose-dependently. However, compared to 80 μmol/L curcumin+HG group, the curcumin+inhibitor group had higher apoptosis rate, LDH release rate, ROS, MDA, Caspase-3 and Bax levels and lower GSH, SOD, Bcl-2, p-AMPK/AMPK, SIRT1 and PGC-1α levels. **Conclusion:** Curcumin can avoid ARPE-19 cells from HG-evoked oxidative injury and it may be connected with the excitation of AMPK/SIRT1 pathway.

**Keywords:** Curcumin, Human Retinal Pigment Epithelial Cells, AMPK, SIRT1, Oxidative Damage.

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**Received:** 12-05-2026;
**Revised:** 09-06-2026;
**Accepted:** 11-08-2026.

## INTRODUCTION

Diabetes can cause chronic damage to multiple tissues and organs such as blood vessels, nerves, eyes and kidneys. Diabetic Retinopathy (DR) and macular disease are microvascular complications of diabetes, which can lead to blindness in severe cases.[1] Retinal Pigment Epithelial (RPE) cells act a pivotal part in retina and are the main cells for maintaining retinal function. Previous studies have shown that hyperglycemia is a key factor for retinopathy in diabetic patients.[2] Long-terms high glucose environment can induce RPE cells to produce excessive oxygen free radicals, resulting in oxidative stress damage.[3] Oxidative stress injury is closely related to retinopathy.[4] Curcumin is a phenolic pigment, which exists in the roots of traditional Chinese medicine such as Curcuma Longa and Radix Curcumae and has pharmacological activities such as antioxidant and hypoglycemic activities.[5,6] Curcumin can protect renal tubular epithelial cells from oxidative stress.[7] At present, the mechanism of curcumin in alleviating oxidative damage of DR is not explicit.[8]

AMP-adenosine activated Protein Kinase (AMPK) is known as a "cellular energy receptor" that improves mitochondrial dysfunction, Silent mating type Information Regulation 2 homolog 1 (SIRT1) could deacetylate many proteins.[9] Zhao *et al.*,[10] showed that activation of AMPK/SIRT1 signaling pathway could refrain the oxidative injury of RPE cells in human. In this study, High Sugar (HG)-caused oxidative damage model of ARPE-19 cells was established and the possible protective effect of curcumin at different doses in human RPE cells (ARPE-19) cell oxidative damage *in vitro* was probed and the potential molecular mechanism of curcumin and correlation with AMPK in improving the oxidative damage in HG-induced ARPE-19 cells was explored, so as to provide certain reference for clinical application on DR treatment, which might be associated with AMPK/SIRT1 pathway.

**DOI:** 10.5530/ijper.20260590

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## MATERIALS AND METHODS

### Drugs

Curcumin (S1848) and AMPK inhibitor (Compound C; S7306) was obtained from Selleck chemicals (USA).

### Cell culture

Human ARPE-19 cells (BFN60807591; ATCC, USA) were cultured in DMEM/F12 medium (21041025; Thermo Fisher Scientific, USA) plus 10% FBS and 100 μ/mL streptomycin and 100 μ/mL penicillin and placed in an incubator for routine culture at 5% $CO_2$ and 37°C.

### CCK8 method

ARPE-19 cells at logarithmic growth stage were split into control group, 20, 40 and 80 μmol/L curcumin groups, therein, the curcumin dosages (20, 40, 80 μmol/L) used was selected according to previously published article,[11] which were cultured in an incubator for 24 hr and then collected. The activity of ARPE-19 cells in each group was tested by CCK-8 kit (CA1210; Solarbio, Beijing) and the operation procedure was according to the kit instructions. Each group has 6 multiple holes and the OD value was tested by microplate reader.

### Cell grouping

ARPE-19 cells in 2.2 were inoculated into a 6-well plate with 6 compound pores in each group and split into following groups: Control group (5 mmol/L glucose), HG group (30 mmol/L glucose,[12] curcumin+HG groups (20, 40, or 80 μmol/L curcumin+30 mmol/L glucose) and curcumin+inhibitor group (80 μmol/L curcumin+30 mmol/L glucose+5 μmol/L AMPK inhibitor.[13] All cells were cultivated for 48 hr for follow-up detection.

### Flow cytometry

Annexin V-FITC/PI Apoptosis kit was obtained from Solarbio (CA1020). Cells from each group in method 2.4 were centrifuged and dissolved in 500 μL binding buffer and later appended of 5 μL AnnexinV-FITC and 5 μL PI for 15 min-incubation in darkness. ARPE-19 cell apoptosis was detected using flow cytometer (FACS-Calibur; Becton Dikinson, USA), 6 replicates were set in each group.

### 2'-7'-Dichlorofluorescin Diacetate (DCFH-DA) probe loading method

Cells of each group in 2.4 were collected, following PBS washing, cells were added of 10 μmol/L DCFH-DA (CA1410; Solarbio) in darkness at 37°C for 30 min, then DCFH-DA was removed and the intracellular ROS level was monitored using flow cytometry after PBS suspension ($1\times10^5$ cells /mL), which was expressed by fluorescence intensity, 6 replicates per group was set.

### ELISA

The contents of SOD, MDA, GSH and LDH in ARPE-19 cell supernatant were detected by corresponding ELISA kits (YS01716B, YS01269B, YS02293B, YS04812B; YaJi Biological, Shanghai).

### Western blot

RIPA lysate was utilized for dissolving each group of cells (30 min) and the cellular supernatant was retained, and protein was quantified with BCA kit (ML4428, Shanghai Enzyme-Linked Biotechnology) and 20 μg protein was used and isolated using 12% SDS-PAGE gel. Later, after protein transfer, PVDF membrane carrying protein was enclosed in skim milk (5%) for 90 min and subsequently rabbit antibodies against Caspase-3 (1:800; ab32351, Abcam, USA), Bax (1:800; ab182733), Bcl-2 (1:800; ab32124), SIRT1 (1:1000; ab12193), PGC-1α (1:1000; ab191838), AMPK (1:1000; ab32508), p-AMPK (1:1000; ab23875) and β-actin (1:1000; ab179467) were introduced and 4°C overnight. TBST was utilized for washing membrane 3 times, diluted HRP-labeled IgG antibody (1:500; ab205718) was added, incubated for 1 hr in ambient temperature, later ECL solution was added after TBST washing and then developed in gel imager (Bio-rad; USA). Image J software was utilized for analyzing the images and computing the gray values of measured proteins with β-actin as inner reference.

### Statistical Methods

GraphPad Prism 8 was utilized for statistical analysis. The measurement data were described by means of mean±standard deviation ($\bar{x}\pm s$), one-way ANOVA was employed to compare multi-group followed by Tukey multiple comparison test using GraphPad Prism 8. $p<0.05$ was deemed to have statistical significance.

## RESULTS

### The influence of curcumin at different doses on ARPE-19 cell activity

For exploring the toxic influence of curcumin on ARPE-19 cells, CCK analysis was conducted. Figure 1 and Table 1 suggested that the difference of cell activity was not noteworthy between 20, 40 or 80 μmol/L curcumin groups and control group, indicating that

**Table 1: Effects of curcumin at different concentrations on ARPE-19 cell activity ($\bar{x}\pm s$, $n=6$).**

| Group | Cell viability (%) |
|---|---|
| Control group | 100.00±0.00 |
| 20 μmol/L Curcumin group. | 98.46±0.19 |
| 40 μmol/L Curcumin group. | 98.35±0.15 |
| 80 μmol/L Curcumin group. | 99.17±0.22 |

Note: [a]$p<0.05$ vs control group.

various dosages of curcumin had no significant impact on cell activity.

## Comparing apoptotic capacity of ARPE-19 cells after different curcumin treatment

Relative to Control group, cell apoptosis rate in HG group was visibly elevated; while cell apoptosis after curcumin (20, 40 or 80 μmol/L) and HG co-treatment was lessened compared with HG group dose-dependently. To explore the mechanism of curcumin in HG-evoked ARPE-19 cell apoptosis, AMPK inhibitor (Compound C) was used. Compared with 80 μmol/L curcumin+HG group, the apoptosis rate was enhanced again after co-treatment of curcumin and AMPK inhibitor in HG-induced ARPE-19 cells (Figure 2 and Table 2). Thus, we concluded that HG could induce ARPE-19 cell apoptosis, while curcumin could avoid ARPE-19 cells from HG-evoked apoptosis, which might be associated with AMPK expression.

## Comparison of oxidative stress indexes of ARPE-19 cells

In comparison with control, the contents of ROS, MDA and LDH in HG group were all elevated, whereas the contents of GSH and SOD were reduced. In comparison with HG group, ROS, MDA and LDH release rates in curcumin (20, 40 or 80 μmol/L)+HG group were decreased, GSH and SOD levels were enhanced, which were dose-dependent. Compared with 80 μmol/L curcumin and HG treatment, the levels of ROS, MDA and LDH after curcumin and inhibitor treatment were elevated, while GSH and SOD were downregulated, as shown in Figure 3 and Table 3. This result indicated that HG might alleviate HG-evoked oxidative damage through affecting AMPK.

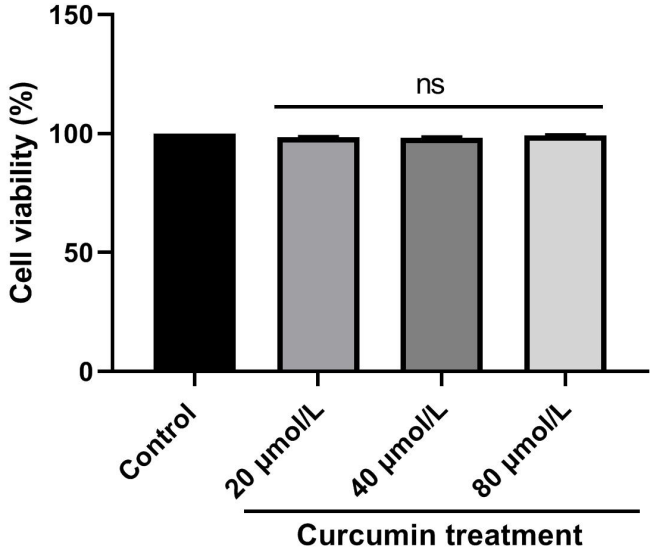


**Figure 1:** Effects of curcumin with multifarious dosages on ARPE-19 cell activity.

## The impact of curcumin on apoptosis-relevant protein expression in HG-induced cells

Relative to control group, Caspase-3 and Bax expression in HG group was elevated and Bcl-2 expression was declined. Compared to HG group, Caspase-3 and Bax after curcumin (20, 40 or 80 μmol/L) treatment in HG-induced cells were downregulated and Bcl-2 was upregulated dose-dependently. Compared with 80 μmol/L curcumin+HG group, the relative abundances of Caspase-3 and Bax in curcumin+inhibitor group were enhanced, whereas Bcl-2 was downregulated (Figure 4 and Table 4). The above results proved that curcumin could dose-dependently regulate the change of HG-induced apoptosis-relevant protein, which might have relevance with AMPK.

## Curcumin might affect HG-evoked ARPE-19 cells through regulating AMPK/SIRT1 pathway

After HG treatment, p-AMPK/AMPK, SIRT1 and PGC-1α were dramatically lowly expressed versus control group. In HG-induced ARPE-19 cells, curcumin (20, 40 or 80 μmol/L) treatment could markedly increase p-AMPK/AMPK, SIRT1 and PGC-1α levels dose-dependently. However, after curcumin and inhibitor co-treatment, p-AMPK/AMPK, SIRT1 and PGC-1α levels were all reduced versus 80 μmol/L curcumin+HG group (Figure 5 and Table 5). From the above, we proved that HG treatment could block AMPK/AMPK pathway in ARPE-19 cells and these effects were mitigated by curcumin dose-dependently. Thus, we deduced that curcumin could retard HG-evoked ARPE-19 cell damage through regulating AMPK/SIRT1 pathway.

# DISCUSSION

As a major complication, DR is the primary reason of visual impairment and blindness in diabetic patients.[14] It has been reported that DR is closely related to oxidative stress and mitochondrial dysfunction and sustained high glucose will cause excessive oxidation of intracellular glucose and induce ROS production, leading to oxidative stress.[15] Therefore, improving antioxidant capacity is a novel orientation for the therapy of DR.

**Table 2: Comparison of ARPE-19 cell apoptosis in each group ($\bar{x}\pm s$, $n$=6).**

| Group | Apoptosis rate (%) |
|---|---|
| Control | 7.15±0.91 |
| HG | 35.15±3.59[a] |
| 20 μmol/L curcumin+HG | 24.16±2.77[b] |
| 40 μmol/L curcumin+HG | 16.48±1.86[bc] |
| 80 μmol/L curcumin+HG | 10.74±1.34[bcd] |
| curcumin+inhibitor | 19.35±2.42[e] |

Note: [a]$p$<0.05 vs control group; [b]$p$<0.05 vs HG group; [c]$p$<0.05 vs 20 μmol/L curcumin+HG group; [d]$p$<0.05 vs 40 μmol/L curcumin+HG group; [e]$p$<0.05 vs 80 μmol/L curcumin+HG group.

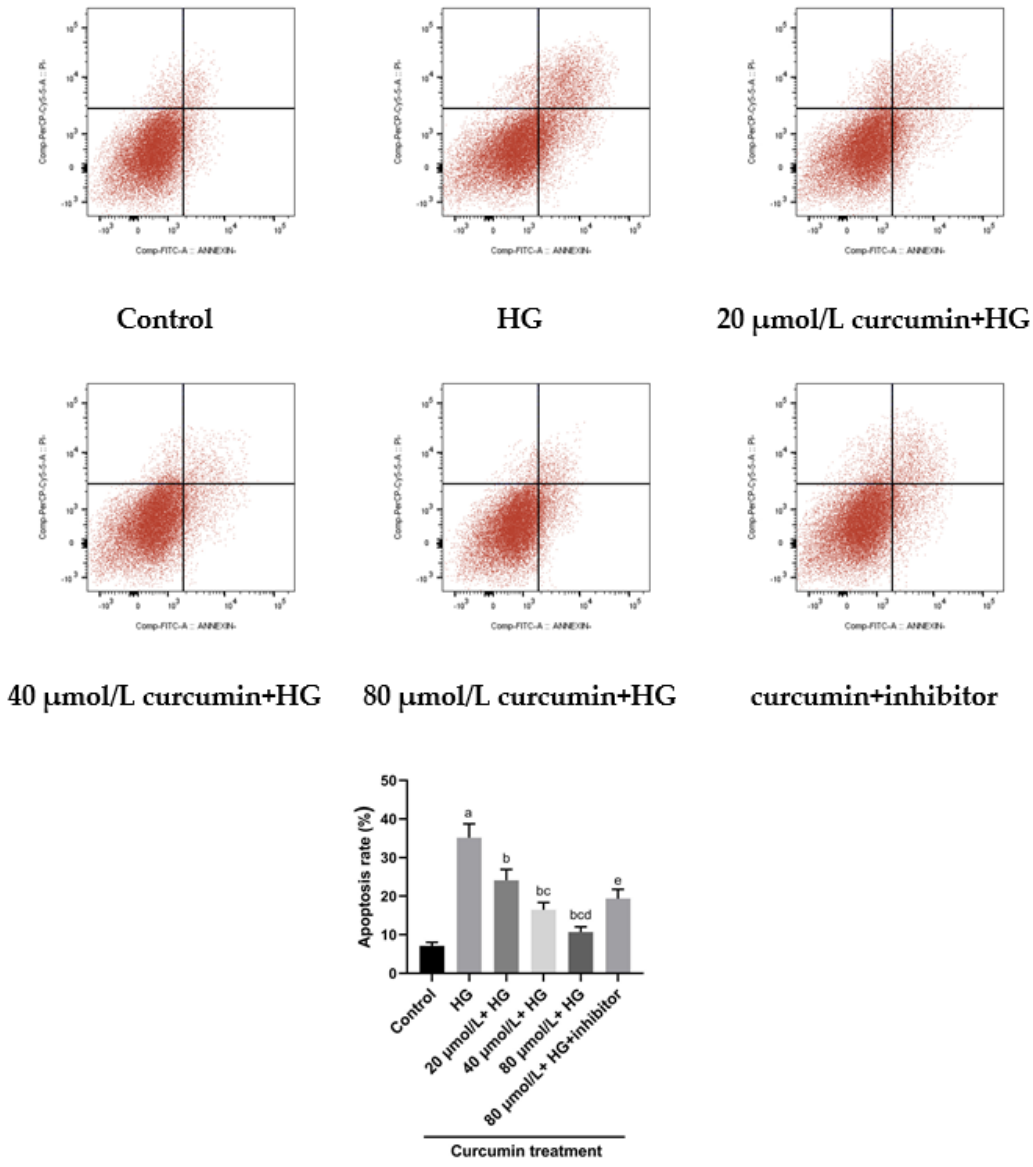


**Figure 2:** Comparison of ARPE-19 cell apoptosis after curcumin treatment.

Curcumin is an acidic phenolic compound extracted from plants such as Zingiberaceae, which has multifarious pharmacological properties including anti-oxidation and regulation of lipid metabolism.[16] Research has reported that curcumin act a certain part in the treatment of diabetes, which can improve the disturbance of retinal photosensitive cell membrane, structural changes of vascular endothelial cells and reduce cell apoptosis caused by diabetes.[17] Curcumin can improve the antioxidant capacity of retina in DR Rats.[8,18] Curcumin can remove oxygen free radicals induced by high sugar in ARPE-19 cells, enhance the antioxidant capacity of cells and inhibit cell apoptosis.[19,20] GSH and SOD are endogenous antioxidants, while MDA are lipid peroxides and their contents respectively represent the antioxidant capacity and oxidation capacity of the body.[21] Tang *et al.*, has proved that Tropisetron could attenuate HG-evoked oxidative stress, cell apoptosis and inflammation in ARPE-19 cells via modulating SIRT1/ROCK1 signaling.[22] And Hu *et al.*, affirmed that CD200R could promote HG-induced oxidative stress and damage in ARPE-19 cells by activating mTOR signaling.[23] Similar to these studies, in this study, the oxidative damage model of human RPE cells was established by HG-induced ARPE-19 cells. And the apoptosis rate, ROS, MDA levels, LDH release rate, Caspase-3 and Bax expression levels of curcumin-treated ARPE-19 cells were dramatically declined versus those in HG group; and GSH, SOD and Bcl-2 levels were overtly increased, indicating that curcumin treatment could enhance the oxidation-resistant ability of ARPE-19 cells and alleviate oxidative damage and inhibit apoptosis of ARPE-19 cells.

Curcumin is an effective activator of AMPK and curcumin can improve diabetes in pregnant mice by activating AMPK.[24] Reports have displayed that curcumin could improve oxidative stress and enhance mitochondrial function by activating AMPK.[25] AMPK

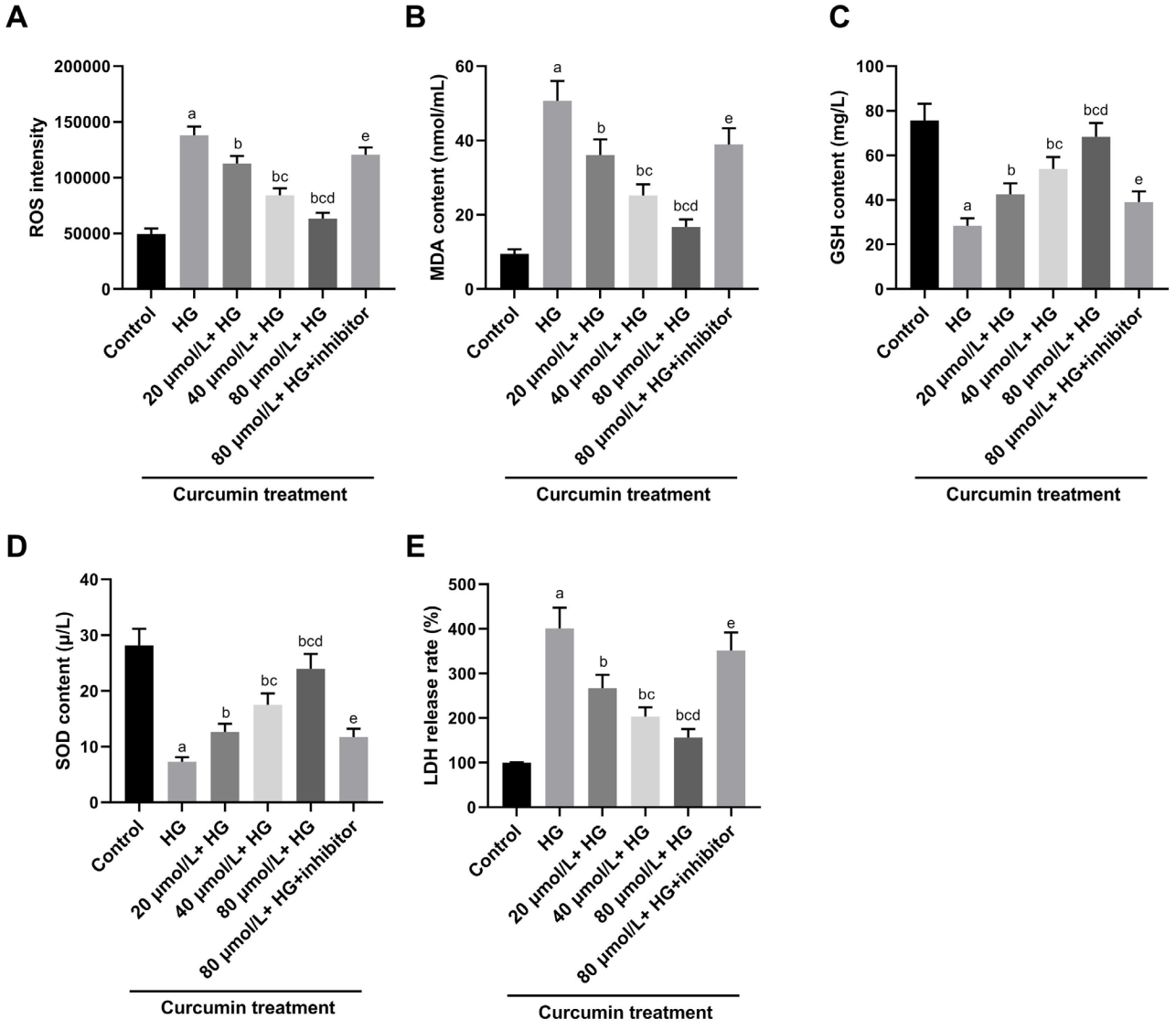


**Figure 3:** The contrast of coefficient of oxidation in ARPE-19 cells.

**Table 3: The contrast of coefficient of oxidation in ARPE-19 cells (x̄±s, *n*=6).**

| Group | ROS intensity | MDA（nmol/mL） | GSH（mg/L） | SOD（μ/L） | LDH release rate（%） |
|---|---|---|---|---|---|
| Control | 49452.84±5035.26 | 9.46±1.24 | 75.59±7.6 | 28.15±3.01 | 99.94±0.51 |
| HG | 138142.46±7643.52[a] | 50.72±5.29[a] | 28.37±3.46[a] | 7.28±0.84[a] | 401.06±46.54[a] |
| 20 μmol/L curcumin+HG | 112601.16±6754.75[b] | 36.06±4.23[b] | 42.43±4.99[b] | 12.64±1.48[b] | 266.85±30.04[b] |
| 40 μmol/L curcumin+HG | 84109.29±6248.54[bc] | 25.19±2.99[bc] | 53.87±5.31[bc] | 17.51±2.03[bc] | 203.42±20.92[bc] |
| 80 μmol/L curcumin+HG | 63245.57±5206.25[bcd] | 16.72±2.06[bcd] | 68.28±6.29[bcd] | 23.94±2.72[bcd] | 156.28±19.46[bcd] |
| curcumin+inhibitor | 120633.55±6381.86[e] | 38.86±4.42[e] | 39.08±4.76[e] | 11.74±1.52[e] | 351.66±40.41[e] |

Note: [a]$p<0.05$ vs control group; [b]$p<0.05$ vs HG group; [c]$p<0.05$ vs 20 μmol/L curcumin+HG group; [d]$p<0.05$ vs 40 μmol/L curcumin+HG group; [e]$p<0.05$ vs 80 μmol/L curcumin+HG group.

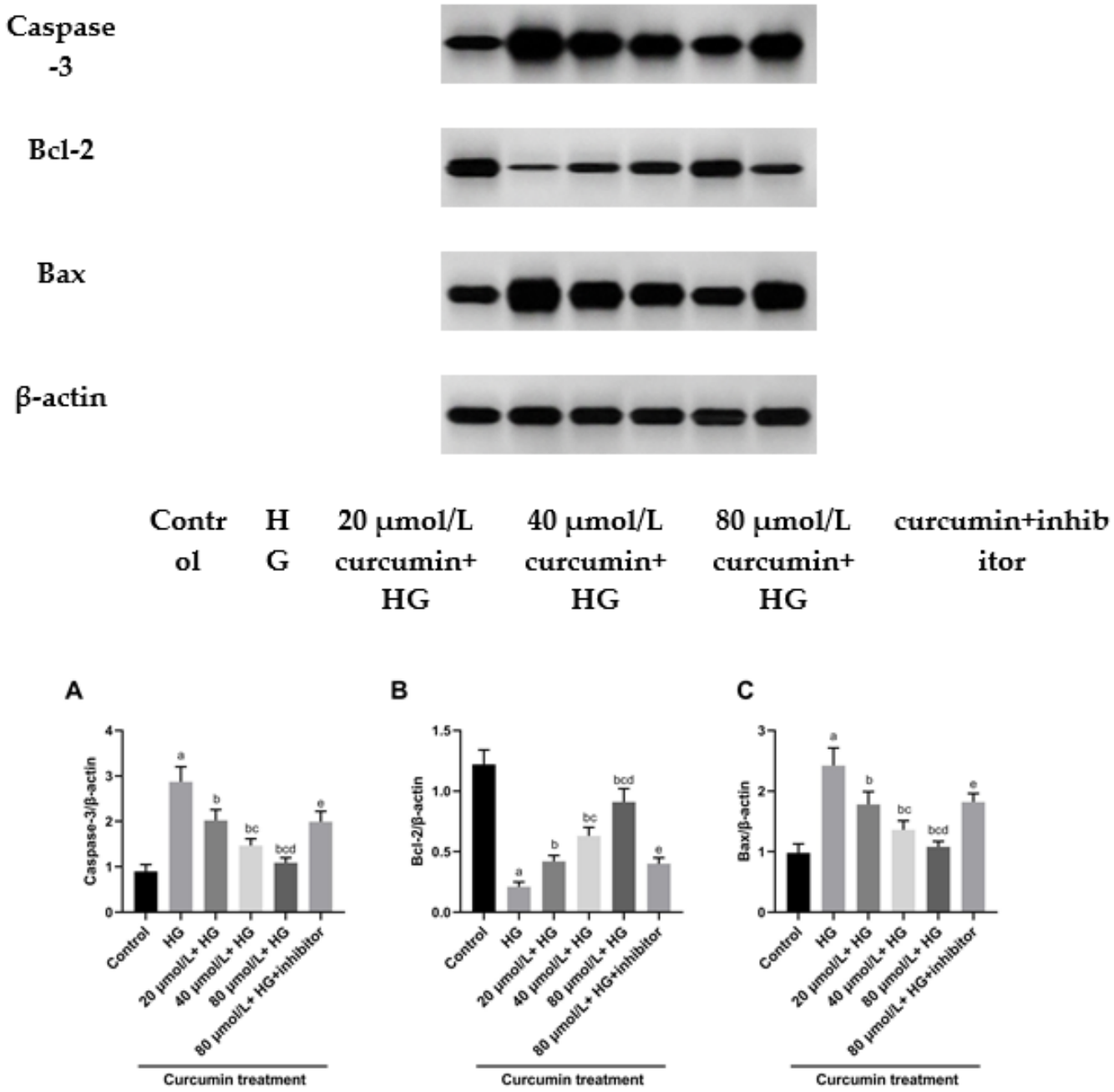


**Figure 4:** Expression of apoptosis-relevant protein levels in HG-evoked cells.

**Table 4: Comparison of apoptosis-relevant protein expression in HG-evoked cells ($\bar{x}\pm s$, $n=6$).**

| Group | Caspase-3/β-actin | Bcl-2/β-actin | Bax/β-actin |
|---|---|---|---|
| Control | 0.90±0.15 | 1.22±0.12 | 0.98±0.15 |
| HG | 2.87±0.33[a] | 0.21±0.04[a] | 2.42±0.29[a] |
| 20 μmol/L curcumin+HG | 2.02±0.24[b] | 0.42±0.05[b] | 1.78±0.21[b] |
| 40 μmol/L curcumin+HG | 1.47±0.15[bc] | 0.63±0.07[bc] | 1.36±0.15[bc] |
| 80 μmol/L curcumin+HG | 1.09±0.11[bcd] | 0.91±0.11[bcd] | 1.08±0.09[bcd] |
| curcumin+inhibitor | 1.99±0.23[e] | 0.40±0.05[e] | 1.82±0.14[e] |

Note: [a]$p<0.05$ vs control group; [b]$p<0.05$ vs HG group; [c]$p<0.05$ vs 20 μmol/L curcumin+HG group; [d]$p<0.05$ vs 40 μmol/L curcumin+HG group; [e]$p<0.05$ vs 80 μmol/L curcumin+HG group.

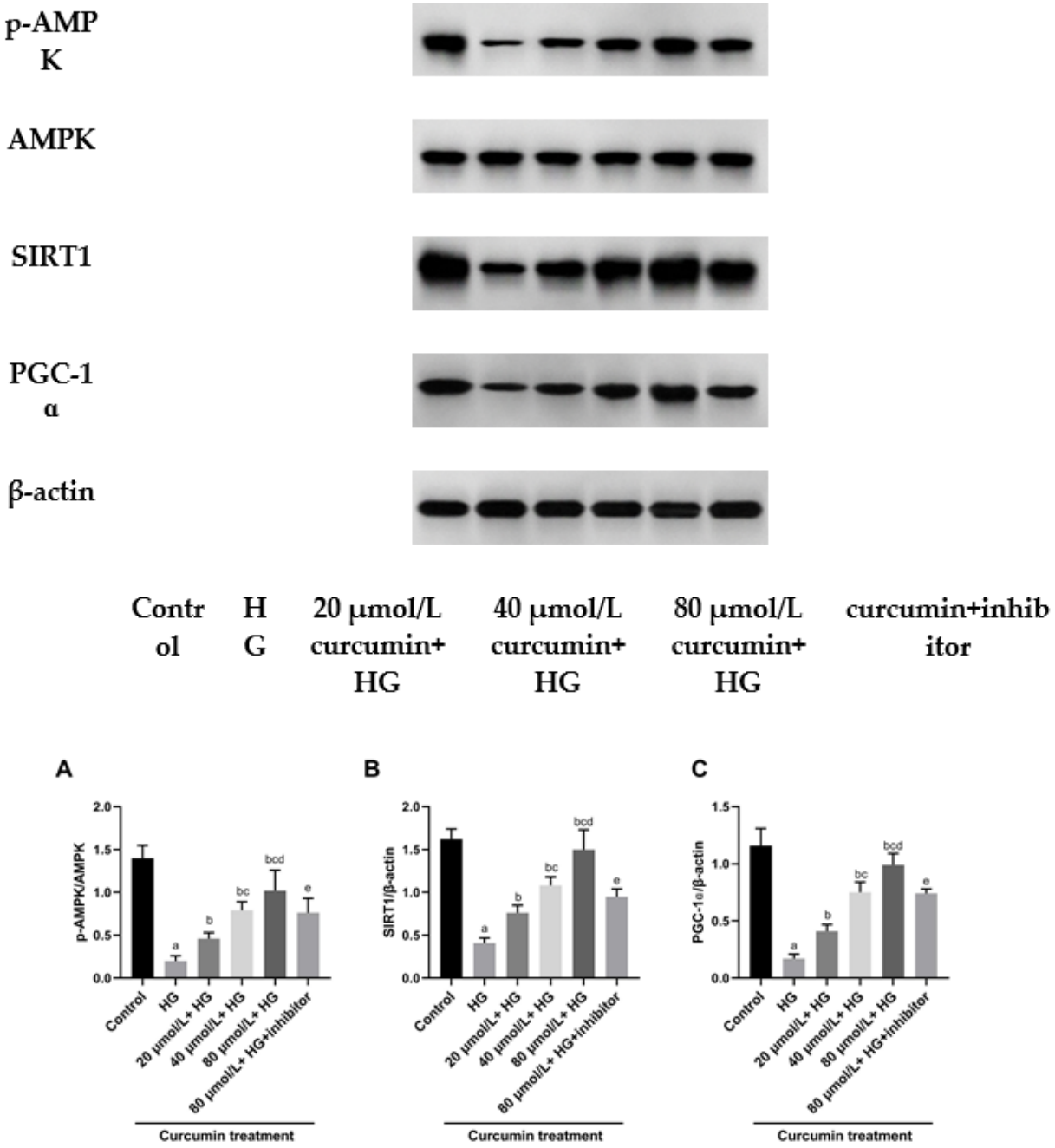


**Figure 5:** Comparison of AMPK/SIRT1 path-relevant protein expression.

**Table 5: Comparison of AMPK/SIRT1 pathway-related protein expression** ($\bar{x}\pm s$, $n$=6).

| Group | p-AMPK/AMPK | SIRT1/β-actin | PGC-1α/β-actin |
|---|---|---|---|
| Control | 1.40±0.15 | 1.62±0.12 | 1.16±0.15 |
| HG | 0.20±0.06[a] | 0.41±0.06[a] | 0.17±0.04[a] |
| 20 μmol/L curcumin+HG | 0.46±0.07[b] | 0.76±0.09[b] | 0.41±0.06[b] |
| 40 μmol/L curcumin+HG | 0.79±0.10[bc] | 1.08±0.10[bc] | 0.75±0.09[bc] |
| 80 μmol/L curcumin+HG | 1.02±0.24[bcd] | 1.50±0.23[bcd] | 0.99±0.10[bcd] |
| curcumin+inhibitor | 0.76±0.17[e] | 0.95±0.09[e] | 0.74±0.04[e] |

Note: [a]$p$<0.05 vs control group; [b]$p$<0.05 vs HG group; [c]$p$<0.05 vs20 μmol/L curcumin+HG group; [d]$p$<0.05 vs 40 μmol/L curcumin+HG group; [e]$p$<0.05 vs 80 μmol/L curcumin+HG group.

is a pivotal factor in regulating bioenergetic metabolism and participates in the oxidative stress process; enhanced expression of AMPK is conducive to cell survival.[26,27] SIRT1 can activate downstream PGC-1α transcription factor through deacetylation to regulate the glucose and lipid metabolism, oxidative stress and cell apoptosis. PGC-1α is a downstream protein regulated by AMPK and SIRT1, which can promote mitochondrial biosynthesis and alleviate cellular oxidative stress by increasing cellular respiration.[28-30] Other reports have manifested that AMPK/SIRT1 path serve a key part in oxidative damage of human RPE cells and activation of AMPK/SIRT1 pathway can refrain human RPE cells from hydrogen peroxide-induced oxidative damage.[31,32] Tang *et al.*, pointed out that Ginsenoside Rd could ameliorate HG-evoked retinal endothelial damage by activating AMPK-STRT1;[33] and Qu *et al.*, confirmed that Metformin could protect ARPE-19 cell from oxidative stress possibly by affecting AMPK/Sirt1.[34]

## CONCLUSION

Here, we manifested that in HG-evoked ARPE-19 cells, curcumin could increase p-AMPK/AMPK, SIRT1 and PGC-1α expression, but inhibiting AMPK could overturn the improvement of oxidative damage induced by curcumin. Meanwhile, the effects of curcumin in cell apoptosis, oxidative damage indexes, Caspase-3 and Bax expression levels in HG-treated ARPE-19 cells were all dramatically mitigated after addition of AMPK inhibitor. The above experiments manifested that curcumin could reduce the oxidative damage of HG-evoked ARPE-19 cells through upregulating AMPK/SIRT1 pathway. In summary, curcumin might inhibit the HG-evoked ARPE-19 cell oxidative damage and improve the antioxidant capacity by activating AMPK/SIRT1 pathway. Although the possible molecular mechanism of curcumin in DR was explained, there are still some shortcomings in our study. For instance, this article didn't set transplantation model in mice and adequate number of patient samples was needful. In our in-depth research, we will execute these above experiments. This report may offer data reference for curcumin and novel thinking in the treatment of retinal pigment epithelial cell damage in DR, but the detailed mechanism of curcumin in regulating AMPK/SIRT1 pathway is still unclear and needs further study.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**DR:** Diabetic retinopathy; **PER:** Retinal pigment epithelial; **AMPK:** AMP-adenosine activated protein kinase; **ROS:** Reactive Oxygen Species; **MDA:** Glutathione; **GSH:** Malondialdehyde; **HRP:** Lactate Dehydrogenase; **LDH:** Horseradish peroxidase; **PVDF:** Polyvinylidene fluoride; **TBST:** Tris-buffered saline with Tween; **ECL:** Enhanced chemiluminescence.

## SUMMARY

In summary, curcumin might inhibit the HG-evoked ARPE-19 cell oxidative damage and improve the antioxidant capacity by activating AMPK/SIRT1 pathway. This report may offer data reference for curcumin in the treatment of DR, but the detailed mechanism of curcumin in regulating AMPK/SIRT1 pathway is still unclear and needs further study.

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**Cite this article:** Bian J, Dong Y, Jiang H, Liu D. Effect of Curcumin on High Glucose-Induced Oxidative Damage of Human Retinal Pigment Epithelial Cells through Regulation of AMPK/SIRT1 Pathway. Indian J of Pharmaceutical Education and Research. 2026;60(4):1523-31.