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Effects of Liver-Smoothing and Spleen-Tonifying Therapy on Malignant Biological Behaviors of HepG2 Cells under Inflammatory Stimulation via Caspase-1 and IRAK1/TRAF6/NF-κB Signaling Pathways

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Abstract: This study aimed to investigate the effects of liver-smoothing and spleen-tonifying therapy on proliferation, invasion, migration and apoptosis of human hepatocellular carcinoma HepG2 cells stimulated by lipopolysaccharide (LPS) combined with adenosine triphosphate (ATP), and preliminarily explore the underlying molecular mechanisms. An in vitro inflammatory cell model was established by treating HepG2 cells with LPS plus ATP. Serum containing low-, medium- and high-dose Xiaoyao San was prepared for intervention, with blank group, model group and Caspase-1 inhibitor VX-765 positive control group set up simultaneously. EdU assay, Transwell invasion test, wound healing assay and Annexin V-APC/7-AAD double staining flow cytometry were adopted to detect cell proliferation, invasion, migration and apoptosis, respectively. Western blot was used to measure the protein expression levels of IRAK1, TRAF6, NF-κB p65 and Caspase-1. The results showed that compared with the blank group, the model group exhibited significantly elevated EdU positive rate, invasive cell number and wound healing rate, markedly reduced cell apoptotic rate, as well as upregulated protein expression of IRAK1, TRAF6, NF-κB p65 and Caspase-1 ($P<0.01$). Relative to the model group, serum containing Xiaoyao San at three doses significantly suppressed proliferation, invasion and migration, promoted apoptosis, and downregulated the expression of the four target proteins ($P<0.01$), with a dose-dependent pharmacological tendency observed. Serum containing Xiaoyao San reverses the malignant biological phenotypes of LPS/ATP-stimulated HepG2 cells by inhibiting cell proliferation, invasion and migration while inducing apoptosis. Its therapeutic effect may be attributed to the suppression of IRAK1/TRAF6/NF-κB p65 and Caspase-1 protein expression, thereby modulating inflammatory signaling cascades.

1. Materials

1.1 Animals and Cell Line

Forty SPF-grade SD rats weighing 200–250 g were purchased from Hunan SJA Laboratory Animal Co., Ltd., with animal production license No. SCXK (Xiang) 2019-0004. All animal experimental protocols were approved by the Animal Ethics Committee of Guangxi University of Chinese Medicine (Approval No. DW20240919-211). Human hepatocellular carcinoma HepG2 cell line (Cat. No. iCell-h092) was obtained from iCell Bioscience Inc. (Shanghai, China).

1.2 Drugs

The composition of Xiaoyao San was as follows: Radix Angelicae Sinensis 30 g, Radix Paeoniae Radix Alba 30 g, Radix Bupleuri 30 g, Poria Cocos 30 g, Rhizoma Atractylodis Macrocephalae 30 g, Radix Glycyrrhizae 15 g, Rhizoma Zingiberis Recens 10 g, Herba Menthae Haplocalycis 10 g. All herbal raw materials were supplied by the First Affiliated Hospital of Guangxi University of Chinese Medicine. Caspase-1 inhibitor VX-765 (Cat. No. HY-13205/CS-2766) was purchased from MCE, USA.

1.3 Reagents

High-glucose complete and incomplete DMEM medium (KGM12800S, KGM12800N, KeyGen Biotech); 1×PBS buffer (0.01 mol/L, pH 7.2–7.4), 0.1% crystal violet staining solution, BCA protein quantification kit and RIPA cell lysis buffer (P1020, G1063, PC0020, R0010, Solarbio); penicillin-streptomycin mixture (A200-100, BDBIO); fetal bovine serum (FBS) and trypsin-EDTA digestion solution (FBS500-H, HYG1111, HYCEZMBIO); electrophoresis buffer, transfer buffer, protein molecular weight marker, rabbit polyclonal primary antibodies against Caspase-1, TRAF6 and NF-κB p65 (G2018, G2017, G2058, GB11383, GB112201, GB11997, Servicebio); EdU cell proliferation detection kit (C0071S, Beyotime); Annexin V-APC/7-AAD apoptosis detection kit (AT105, MultiSciences); ultra-sensitive ECL chemiluminescence reagent (BL520A, Biosharp); anti-IRAK1 polyclonal antibody (PAB58210, Bioswamp); anti-GAPDH primary antibody (BL006B, Biosharp).

1.4 Instruments

1.3 m Class II biosafety cabinet (MCB-1300VA9N, Meiling); inverted fluorescence microscope imaging system (MF53, Mshot); multi-functional microplate reader (INFINITE 200PRO, TECAN); medical centrifuge for 15/50 mL tubes (4-5y, Hengnuo); low-temperature high-speed centrifuge (SLX-1024F, Servicebio); CO_2 incubator (3131, Thermo Fisher Scientific); vertical electrophoresis system (PowerPac Basic, Bio-Rad); horizontal shaker (TS-3D, Kylin-Bell); low-temperature high-speed tissue homogenizer (KZ-III-F, Servicebio); gel imaging system (Tanon 5200, Tanon); flow cytometer (CytoFLEX, Beckman Coulter).

2. Methods

2.1 Preparation of Serum Containing Herbal Medicine

Serum containing Xiaoyao San was prepared following standard protocols specified in *Methodology of Chinese Herbal Pharmacological Experiments*[1]. Forty SD rats were acclimatized for 1 week and randomly divided into blank serum group, low-, medium- and high-dose Xiaoyao

San serum groups, with 10 rats per group. Rats in the three medication groups were intragastrically administered Xiaoyao San decoction at doses of 9.25, 18.5 and 37 $g \cdot kg^{-1}$ twice daily for 3 consecutive days, with a constant administration volume of 10 $mL \cdot kg^{-1}$. The blank group received an equal volume of normal saline. Abdominal aortic blood was collected 1 h after the last gavage. Blood samples were kept at room temperature for 30 min, then centrifuged at 3000 $r \cdot min^{-1}$ for 10 min at 4 ℃ to separate serum. The serum was inactivated in a 56 ℃ water bath for 30 min, sterile-filtered through a 0.22 μm microporous membrane, aliquoted and stored at −80 °C for subsequent use.

2.2 Cell Culture

Human HepG2 cells were cultured in high-glucose DMEM medium supplemented with 10% FBS and 1% penicillin-streptomycin, maintained at 37 °C in a humidified incubator with 5% CO_2. Cells were passaged every 2–3 d using 0.25% trypsin-EDTA digestion when reaching 80%–90% confluence. Cells at logarithmic growth phase were harvested for all subsequent experiments. During intervention, FBS in culture medium was replaced with corresponding blank serum or Xiaoyao San-containing serum at a fixed proportion.

2.3 Establishment of HepG2 Inflammatory Stimulation Model

Logarithmic-phase HepG2 cells were digested to prepare single-cell suspension, adjusted to a density of 1×10^4 cells/well and seeded into 96-well plates. After cells adhered and reached 70%–80% confluence, the original medium was discarded and replaced with medium containing 1% blank serum plus LPS at a final concentration of 100 $ng \cdot mL^{-1}$ for 12 h incubation. The medium was then replaced with serum-free DMEM containing ATP (final concentration 5 $mmol \cdot L^{-1}$) for another 6 h to construct the LPS/ATP-induced inflammatory stimulation model.

2.4 Grouping and Intervention Treatment

Six experimental groups were set up: blank group, model group, positive control group, low-dose Xiaoyao San group, medium-dose Xiaoyao San group and high-dose Xiaoyao San group.

1) Blank group: Incubated with DMEM medium containing 15% blank serum without any inflammatory stimulation.

2) Model group: Cells were subjected to LPS/ATP stimulation as described in Section 2.3, followed by culture with DMEM medium containing 15% blank serum.

3) Positive control group: Cells were modeled identically to the model group, then cultured with medium supplemented with 10 $\mu mol \cdot L^{-1}$ VX-765 and 15% blank serum.

4) Low/medium/high-dose Xiaoyao San groups: Cells were modeled identically to the model group, then cultured with DMEM medium containing 15% low-, medium-, high-dose Xiaoyao San-containing serum respectively.

2.5 Detection of Experimental Indicators

2.5.1 EdU Assay for Cell Proliferation

HepG2 cells at logarithmic phase were seeded into culture plates and treated according to grouping protocols for 24 h. EdU working solution was added and incubated following the kit instructions. After fixation, permeabilization and fluorescent staining in the dark, three random fields were captured under a fluorescence microscope. The number of EdU-positive cells and total cells were counted to calculate the EdU positive rate: EdU positive rate (%) = (Number of

EdU-positive cells / Total cell number) × 100%.

2.5.2 Transwell Assay for Cell Invasion

Transwell chambers pre-coated with Matrigel were placed in 24-well plates. Digested cells were resuspended to a density of 4×10^5 cells·mL^{-1}, and 200 μL cell suspension was added to the upper chamber, while 500 μL DMEM medium with 10% FBS was added to the lower chamber as chemoattractant. After 24 h incubation, cells were washed with PBS, fixed with 4% paraformaldehyde and stained with 0.1% crystal violet. Cells remaining on the upper membrane surface were wiped off with cotton swabs. Three random fields were photographed under an inverted microscope to count invasive cells; the experiment was repeated three times to obtain average values.

2.5.3 Wound Healing Assay for Cell Migration

Logarithmic-phase HepG2 cells were seeded into 6-well plates and cultured until full confluence (90%–100%). A straight scratch was drawn across the cell monolayer using a sterile 200 μL pipette tip. After PBS washing, serum-free DMEM medium was added for grouped intervention. Images of the scratch area were captured at 0 h and 24 h post-intervention. ImageJ software was used to quantify scratch area, and wound healing rate was calculated as follows: Wound healing rate (%) = [(Scratch area at 0 h − Scratch area at 24 h) / Scratch area at 0 h] × 100%.

2.5.4 Annexin V-APC/7-AAD Flow Cytometry for Apoptosis Detection

After 24 h grouped intervention, cells were washed twice with pre-cooled PBS, and 1×10^6 cells were collected per group. Cell pellets were resuspended in 500 μL pre-cooled 1× Binding Buffer, mixed with 5 μL Annexin V-APC and 10 μL 7-AAD, and incubated at room temperature in the dark for 5 min before immediate flow cytometry detection.

- Viable cells: Annexin V-APC$^-$, 7-AAD$^-$
- Early apoptotic cells: Annexin V-APC$^+$, 7-AAD$^-$
- Late apoptotic/necrotic cells: Annexin V-APC$^+$, 7-AAD$^+$ Total apoptotic rate = Percentage of early apoptotic cells + Percentage of late apoptotic/necrotic cells.

2.5.5 Western Blot for Protein Expression of Caspase-1, IRAK1, TRAF6 and NF-κB p65

After 24 h intervention, total cellular protein was extracted using RIPA lysis buffer on ice for 20 min. Lysates were centrifuged at 12000 r·min^{-1} for 10 min at 4 °C to collect supernatant. Protein concentration was quantified via BCA assay, normalized, mixed with protein loading buffer and denatured at 95 ℃ for 5 min. Equal amounts of protein were separated by SDS-PAGE electrophoresis and transferred onto methanol-activated PVDF membranes. Membranes were blocked with 5% skim milk powder at room temperature for 1 h, then incubated with primary antibodies (anti-Caspase-1, anti-IRAK1, anti-TRAF6, anti-NF-κB p65 and anti-GAPDH) overnight at 4 ℃. After TBST washing, membranes were incubated with HRP-conjugated anti-rabbit IgG secondary antibody at room temperature for 1 h. Following repeated TBST washing, ECL chemiluminescence substrate was applied for signal development, and band images were captured with a gel imaging system. ImageJ software was used to analyze gray value of each target band normalized to GAPDH internal reference.

2.6 Statistical Analysis

Statistical analysis was performed using SPSS 25.0 software. Measurement data were expressed

as mean ± standard deviation ($\bar{x}\pm s$). Normality and homogeneity of variance tests were conducted prior to intergroup comparison. One-way analysis of variance (ANOVA) was adopted for normally distributed data with homogeneous variance, followed by appropriate post-hoc multiple comparison tests. $P<0.05$ was defined as statistically significant difference.

3. Results

3.1 Effects of Liver-Smoothing and Spleen-Tonifying Therapy on Proliferation of LPS/ATP-Stimulated HepG2 Cells

As shown in Figure 1 and Table 1, after 24 h intervention, the EdU positive rate of HepG2 cells in the model group was significantly higher than that in the blank group ($P<0.01$), indicating LPS/ATP stimulation markedly promoted cell proliferation. Compared with the model group, all three doses of Xiaoyao San serum significantly reduced EdU positive rate ($P<0.01$), with proliferation inhibitory effect enhanced dose-dependently, and the high-dose group exerted the strongest activity.

Table 1: Effects of Xiaoyao San on Malignant Phenotypes of HepG2 Cells

No.	Group	EdU Positive Rate (%)	Number of Invasive Cells	Wound Healing Rate (%)	Apoptotic Rate (%)
A	Blank Group	41.22 ±4.55	1254.33 ±47.12	33.95 ±4.41	17.31 ±2.16
B	Model Group	70.96 ±4.36**	2532.00 ±198.82**	85.17 ±8.43**	4.69 ±0.94**
C	Low-Dose Group	58.13 ±6.74##	1841.67 ±210.51##	54.12 ±5.64##	10.42 ±1.17##
D	Medium-Dose Group	44.18 ±7.86##	1459.67 ±57.05##	43.69 ±4.93##	13.56 ±1.42##
E	High-Dose Group	25.37 ±2.30##	647.00 ±172.6##	13.37 ±1.83##	25.77 ±2.40##
F	Positive Control Group	36.32 ±3.95##	970.67 ±221.43##	23.92 ±3.42##	17.60 ±1.91##

P<0.01 vs. Blank Group; ##P<0.01 vs. Model Group

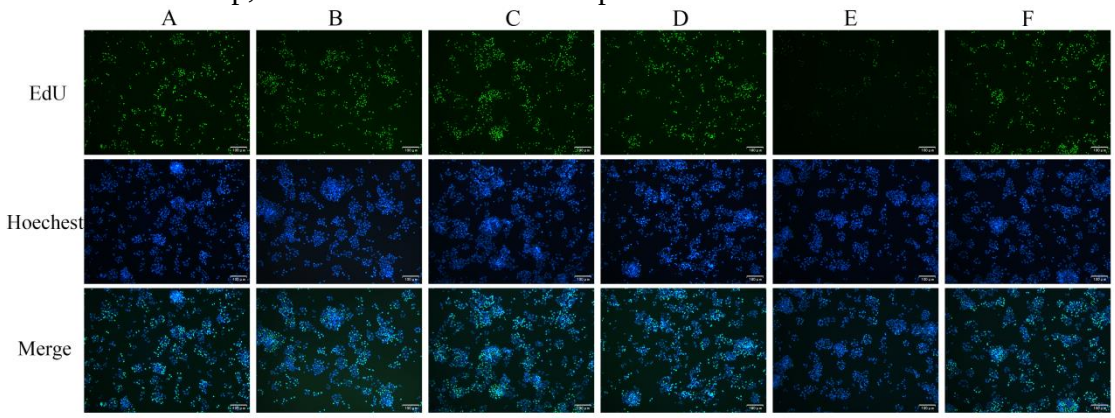

Figure 1: Comparison of Cell Proliferation Across Groups

Notes: A: Blank Group; B: Model Group; C: Low-Dose Group; D: Medium-Dose Group; E: High-Dose Group; F: Positive Control Group

3.2 Effects of Liver-Smoothing and Spleen-Tonifying Therapy on Invasion of LPS/ATP-Stimulated HepG2 Cells

Transwell invasion results (Figure 2, Table 1) demonstrated that the number of invasive cells in

the model group was significantly elevated relative to the blank group (P<0.01), proving LPS/ATP stimulation strengthened the invasive capacity of HepG2 cells. Versus the model group, low-, medium- and high-dose Xiaoyao San serum all significantly decreased invasive cell count (P<0.01), with invasive inhibition positively correlated with serum concentration, and the high-dose group showed optimal efficacy.

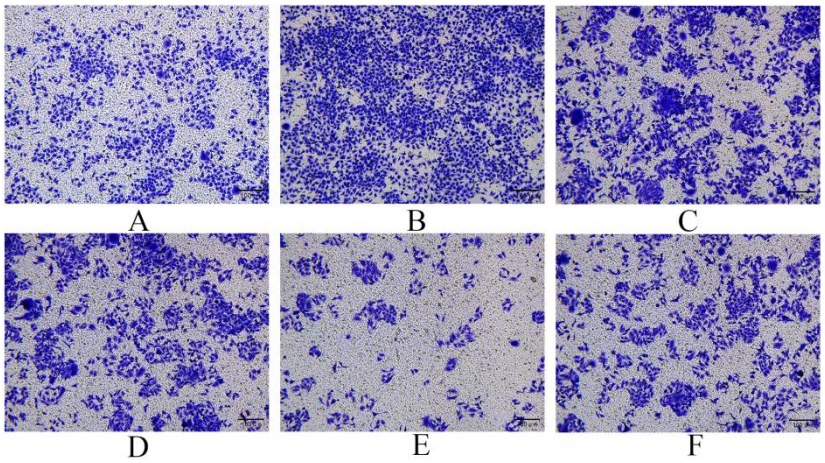

Figure 2: Comparison of Cell Invasion Across Groups

Notes: A: Blank Group; B: Model Group; C: Low-Dose Group; D: Medium-Dose Group; E: High-Dose Group; F: Positive Control Group

3.3 Effects of Liver-Smoothing and Spleen-Tonifying Therapy on Migration of LPS/ATP-Stimulated HepG2 Cells

Wound healing assay results (Figure 3, Table 1) revealed that wound healing rate was significantly higher in the model group than the blank group (P<0.01), suggesting LPS/ATP enhanced cell migratory ability. All three Xiaoyao San serum concentrations markedly lowered wound healing rate compared with the model group (P<0.01), with migration suppression intensified as dosage increased, peaking in the high-dose group.

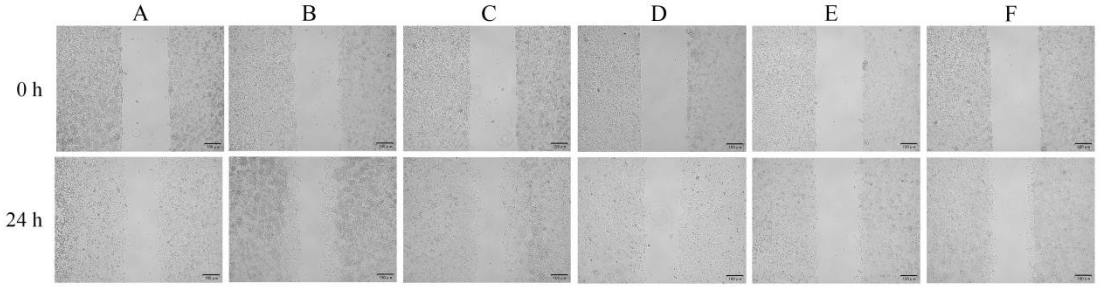

Figure 3: Comparison of Cell Migration across Groups

Notes: A: Blank Group; B: Model Group; C: Low-Dose Group; D: Medium-Dose Group; E: High-Dose Group; F: Positive Control Group

3.4 Effects of Liver-Smoothing and Spleen-Tonifying Therapy on Apoptosis of LPS/ATP-Stimulated HepG2 Cells

After 24 h intervention (Figure 4, Table 1), the model group exhibited significantly reduced apoptotic rate compared with the blank group (P<0.01), indicating inflammatory stimulation

suppressed HepG2 cell apoptosis. All Xiaoyao San serum groups displayed significantly elevated apoptotic rates relative to the model group (P<0.01), with pro-apoptotic effect enhanced dose-dependently, and the high-dose group achieved the strongest apoptosis induction.

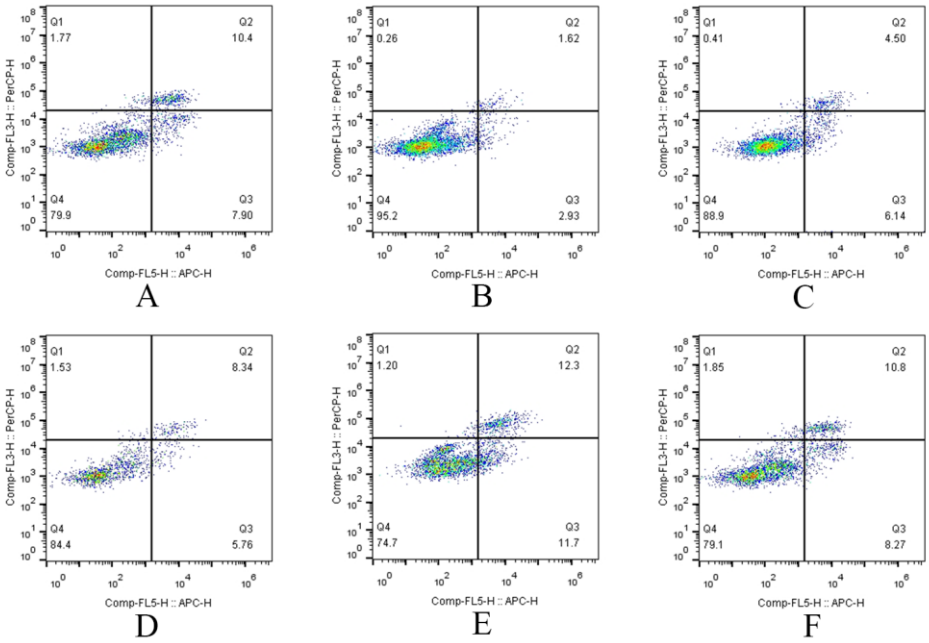

Figure 4: Flow Cytometry Apoptosis Scatter Plots Across Groups

Notes: A: Blank Group; B: Model Group; C: Low-Dose Group; D: Medium-Dose Group; E: High-Dose Group; F: Positive Control Group

3.5 Effects of Liver-Smoothing and Spleen-Tonifying Therapy on Expression of Inflammation-Related Proteins in LPS/ATP-Stimulated HepG2 Cells

Western blot outcomes (Figure 5, Table 2) showed that the relative expression levels of IRAK1, TRAF6, NF-κB p65 and Caspase-1 were all significantly upregulated in the model group versus the blank group (P<0.01), confirming LPS/ATP stimulation activated the expression of these inflammatory mediators. Compared with the model group, all three Xiaoyao San serum concentrations significantly downregulated the four target proteins (P<0.01), with more pronounced inhibitory effects observed at higher doses. The protein expression levels in the high-dose group were close to those in the blank group and VX-765 positive control group.

Table 2: Effects of Xiaoyao San on Relative Expression of Inflammation-Related Proteins

No.	Group	IRAK1	NF-κB p65	TRAF6	Caspase-1
A	Blank Group	0.30 ±0.04	0.29 ±0.03	0.45 ±0.03	0.39 ±0.03
B	Model Group	0.90 ±0.07**	0.85 ±0.09**	0.99 ±0.07**	0.94 ±0.07**
C	Low-Dose Group	0.63 ±0.04##	0.67 ±0.06##	0.81 ±0.07##	0.79 ±0.06##
D	Medium-Dose Group	0.51 ±0.05##	0.49 ±0.06##	0.67 ±0.05##	0.62 ±0.05##
E	High-Dose Group	0.34 ±0.03##	0.33 ±0.06##	0.47 ±0.04##	0.42 ±0.04##
F	Positive Control Group	0.37 ±0.04##	0.37 ±0.05##	0.52 ±0.06##	0.44 ±0.03##

P<0.01 vs. Blank Group; ##P<0.01 vs. Model Group

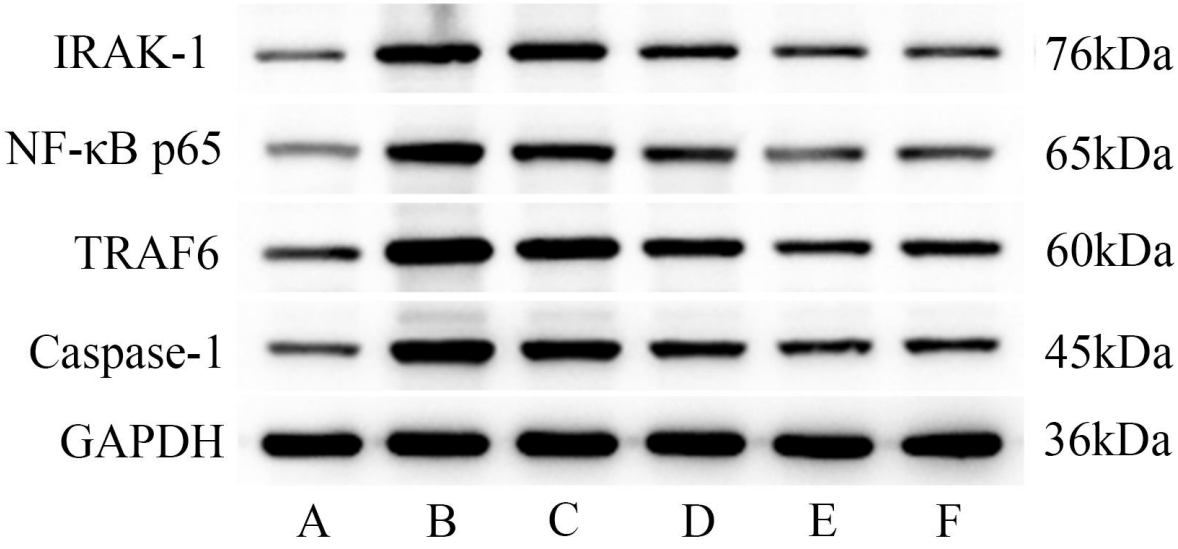

Figure 5: Western Blot Bands of Target Proteins Across Groups

Notes: A: Blank Group; B: Model Group; C: Low-Dose Group; D: Medium-Dose Group; E: High-Dose Group; F: Positive Control Group

4. Discussion

Persistent hepatic inflammation is a core microenvironmental driver of hepatocellular carcinoma initiation and progression. Combined LPS and ATP treatment activates pyroptosis-associated signaling, endowing hepatocytes with enhanced proliferation, invasion and migration capacities alongside suppressed apoptosis-this malignant phenotype closely recapitulates the pathological progression from chronic liver disease to hepatocellular carcinoma in clinical practice[2]. The LPS/ATP stimulation system adopted in this study reliably mimics the in vitro pathological state of inflammation-driven hepatocellular carcinoma deterioration[3].

The IRAK1/TRAF6/NF-κB cascade represents a canonical inflammatory signaling axis. Upon exogenous stimulation, activated IRAK1 binds and triggers TRAF6, which further mediates nuclear translocation of NF-κB p65 to initiate transcription of abundant pro-inflammatory cytokines, thereby amplifying local inflammatory responses persistently[4]. Meanwhile, activation of this pathway concurrently upregulates Caspase-1 to activate pyroptosis, and the synergistic effects of inflammatory cascade and pyroptosis jointly aggravate malignant transformation of hepatocytes[5]. Consistent with this mechanism, our data revealed drastically elevated IRAK1, TRAF6, NF-κB p65 and Caspase-1 protein expression in the model group, accompanied by intensified proliferative, invasive and migratory activities and reduced apoptosis, which validated that overactivation of this signaling axis promotes malignant biological behaviors of hepatocellular carcinoma cells.

Liver-smoothing and spleen-tonifying therapy serves as the core therapeutic strategy for liver disease with liver stagnation and spleen deficiency syndrome, represented by Xiaoyao San which concurrently disperses liver qi, tonifies spleen and nourishes blood. This formula is widely applied in clinical adjuvant treatment of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma[6]. In this study, serum containing serially diluted Xiaoyao San was used to intervene inflammatory injured hepatocellular carcinoma cells. The results demonstrated that herbal serum exerted dose-dependent inhibition on HepG2 proliferation, invasion and migration while elevating apoptotic rate, accompanied by downregulation of IRAK1, TRAF6, NF-κB p65 and Caspase-1 expression. The regulatory efficacy of high-dose Xiaoyao San was comparable to VX-765, a specific Caspase-1

inhibitor, indicating that Xiaoyao San alleviates inflammatory microenvironment and suppresses hepatocellular carcinoma progression mainly via inhibiting the IRAK1/TRAF6/NF-κB pathway and reducing Caspase-1 expression[7].

Existing research on Xiaoyao San mostly focuses on its anti-inflammatory or anti-tumor activity separately, lacking integrated verification linking anti-inflammation and anti-cancer effects under inflammatory microenvironment with multi-target signaling detection[8]. The present study synchronously characterized cellular malignant phenotypes and multiple key inflammatory proteins, systematically elucidating the molecular mechanism of liver-smoothing and spleen-tonifying herbal formula against inflammation-mediated hepatocellular carcinoma progression. Nevertheless, several limitations remain: all experiments were conducted in vitro without in vivo animal models to validate pharmacological efficacy[9]; downstream inflammatory cytokine secretion was not detected, failing to fully delineate the complete upstream and downstream regulatory chain. Follow-up research will establish animal models combining liver stagnation-spleen deficiency and inflammatory liver injury, supplement tissue pathological examination and serum inflammatory cytokine quantification to refine the in vivo mechanism of Xiaoyao San, providing more comprehensive experimental evidence for its clinical application in hepatocellular carcinoma with liver stagnation and spleen deficiency syndrome[10].

5. Conclusion

Combined LPS/ATP stimulation constructs an inflammatory microenvironment in HepG2 cells, activates the IRAK1/TRAF6/NF-κB signaling axis and Caspase-1, and significantly facilitates proliferation, invasion and migration while restraining apoptosis of hepatocellular carcinoma cells. Serum containing Xiaoyao San reverses inflammation-induced malignant biological behaviors of HepG2 cells-including suppressed proliferation, invasion and migration, and enhanced apoptosis-by downregulating IRAK1, TRAF6, NF-κB p65 and Caspase-1 protein expression to block excessive activation of inflammatory signaling, with obvious dose-dependent pharmacological activity. Liver-smoothing and spleen-tonifying therapy effectively mitigates inflammation-mediated deterioration of hepatocellular carcinoma cells via modulation of the IRAK1/TRAF6/NF-κB/Caspase-1 inflammatory signaling cascade, providing in vitro experimental support for the clinical use of Xiaoyao San in inflammatory hepatocellular carcinoma with liver stagnation and spleen deficiency syndrome.

Acknowledgement

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