Effects of Resveratrol on Hepatitis B Virus Replication: In vitro and in vivo Experiments

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Keywords
Hepatitis B virus · Resveratrol · miR-155 · Autophagy · Virus replication

Abstract
Introduction: Hepatitis B virus (HBV) infection is a disease with high incidence and lack of effective treatment. In this study, we further explored the mechanism of resveratrol (RVT) in the inhibition of HBV replication. The effects of RVT on HBV replication were verified using in vitro and in vivo experiments. Methods: HepG2 and HepG2.2.15 cell lines were cultured in vitro, and different concentrations of RVT were used to determine its effect on the proliferation of the two cell lines. Autophagy agonists and inhibitors were given, and whether RVT exerts its effect on the proliferation of HepG2 and HepG2.2.15 cells through autophagy was determined. Reverse transcription-quantitative polymerase chain reaction and Western blot were used to detect changes in autophagy-related factors LC3-II, LC3-I, Beclin 1, and p62. Through transfection of pmiR-155, shmiR-155, and the corresponding control group, the relevant mechanism of RVT in inhibiting the proliferation of HepG2 and HepG2.2.15 cells was analyzed. RVT inhibited the toxicity for HepG2.2.15 cells and reduced HBV replication in vitro (p < 0.05). This effect of RVT was enhanced by rapamycin (RAPA; autophagy activator; p < 0.05) but was partially reversed by 3-MA (autophagy inhibitor; p < 0.05). In addition, our results showed that miR-155 expression was higher in HepG2.2.15 cells than in HepG cells (p < 0.05). miR-155 expression in the RVT treatment group was significantly reduced (p < 0.05). We designed an miR-155 overexpression plasmid, low miR-155 expression plasmid, and the corresponding negative control for transfection and found that transfection of pmiR-155 can partially reverse the effect of RVT (p < 0.05), while transfection with shmiR-155 can enhance the effect of RVT (p < 0.05). Discussion: RVT inhibits miR-155, activates autophagy, inhibits the toxicity for HepG2.2.15 cells, and reduces HBV replication, providing a new research direction for the treatment of HBV infection.

Introduction
Hepatitis B virus (HBV) infection is a serious global public health problem [1]. Current epidemiological statistics show that approximately 2 billion people worldwide have been infected with HBV, and approximately...
350 million people have chronic HBV infection [2]. Massive replication of HBV can cause severe liver damage, which can lead to secondary acute severe hepatitis, cirrhosis, and liver failure, among others [3]. In addition, chronic HBV infection is the main cause of hepatocellular carcinoma (HCC) [4]. According to epidemiological statistics, approximately 1 million people die from HBV-related liver disease annually [5]. The current first-line drugs for the treatment of HBV include interferon (interferon-α, IFN-α) and nucleoside (acid) analogs [6]. While these drugs can greatly reduce HBV replication, they still cannot cure hepatitis B [7, 8]. Therefore, exploring new drugs that inhibit HBV DNA replication to protect patients with hepatitis B is currently one of the most important strategies for treating HBV and reducing liver damage.

Resveratrol (RVT) is a class of polyphenolic compounds found in Polygonum cuspidatum, grapes, peanuts, mulberries, and other plants. Studies have shown that RVT has a good therapeutic effect in many diseases [9]. For example, in a bacterial meningitis model, RVT exhibited antineuronal pyrolysis and apoptosis by regulating the expression level of miRNAs [10]. In recent years, an increasing number of studies have reported the various effects of RVT on viral infections. For example, RVT can antagonize respiratory syncytial virus infection by inhibiting the TRIF/TBK1/IRF.3 complex [11]. It is also effective in the treatment of influenza and severe acute respiratory syndrome [12]. In addition, it can synergistically enhance the efficacy of antihuman immunodeficiency virus and herpes simplex virus drugs [13]. Studies have reported that RVT can inhibit the replication of HBV, which is beneficial for the protection of liver function in patients with HBV. However, some studies believe that RVT may aggravate the development of hepatitis B, and patients with hepatitis B infection should be cautious in taking RVT as diet supplements [14]. Therefore, this study aimed to verify the effects of RVT on HBV replication using in vivo and in vitro experiments and further analyze the mechanism of its generation.

Material and Methods

Cell Culture

HepG2 and HepG2.2.15 cell lines were purchased from the Type Culture Center of the Chinese Academy of Sciences (Shanghai, China). They were cultured at 37°C in a 5% CO₂ incubator. HepG2 cells were cultured in minimal essential medium (MEM) containing 10% fetal bovine serum (FBS), 100 U/L penicillin, and 100 U/L streptomycin, while HepG2.2.15 cells were cultured in Dulbecco’s modified Eagle medium containing 10% FBS, 100 U/L penicillin, and 100 U/L streptomycin. This study was approved by the Ethics Committee of the Guangzhou Qite Biotechnology Co., Ltd. (approval number: ChiCTR1900123254).

Plasmids and Transfection

Specific small interfering (si) RNA (simiR-155) and negative control (siNC) targeting miR-155 expression were synthesized by Wuhan Genesil Biotechnology Co., Ltd. (Wuhan, China). The miR-155 overexpression plasmid pmir-155 and empty plasmids pMR-mCherry, shmiR-155, and sh-NC were produced by the Chinese Academy of Sciences (Changchun, China).

Following the manufacturer’s instructions, all plasmids were transfected into cells using Lipofectamine 2000 (Invitrogen, Thermo Fisher Scientific, Inc., Waltham, MA, USA). The transfection efficiency was evaluated by real-time PCR.

Enzyme-Linked Immunosorbent Assay for Detection of HBsAg in Cell Supernatant

The sample was diluted with PBS 10 times and mixed well, and 75 μL of the diluted sample was added to each well in duplicate. Wells for controls were allocated as follows: three negative controls, two positive controls, and one blank control. Enzyme-linked immunosorbent assay (ELISA) was performed according to the manufacturer’s instructions (i.e., with slight shaking). The reaction plate was slightly shaken for 10 s, sealed, and incubated at 37°C for 1 h. After incubation, 50 μL of enzyme conjugate was added to each well, and the reaction plate was slightly shaken for 10 s, sealed, and incubated at 37°C for 30 min. The reaction plate was then washed five times with a plate washer and thoroughly patted dry on the bench. Chromogenic reagent A and B (each 50 μL) were added to each well, and the plates were incubated at 37°C for 30 min. After incubation, 50 μL of stop solution was added to each well. After slight shaking and mixing, the absorbance was measured at a wavelength of 450 nm using a microplate reader (SpectraMax M5; Molecular Devices, San Jose, CA, USA).

Cytotoxicity Test

After cell treatment for 3 days, the reagents were stored at 4°C to melt, and the reaction solution (MTS: PMS = 20:1) was prepared. The cell supernatant was aspirated and discarded. Meanwhile, the pellet was washed with PBS twice, and 20 μL of reaction solution and 100 μL of medium were added to individual wells of a 96-well plate in triplicate and then incubated at 37°C for 1–4 h. After incubation, the absorbance was measured at a wavelength of 490 nm using a microplate reader, and the data were recorded and the result was calculated.

3-(4,5-Dimethyl-2-Thiazolyl)-2,5-Diphenyl-2-H-Tetrazolium Bromide Assay

In total, 100 μL of cell suspension containing 1,000 cells was inoculated into a 96-well plate and incubated at 37°C and 5% CO₂ for 0, 24, 48, and 72 h. The 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide assay was performed at the indicated time points to determine cell proliferation. Twenty microliters of 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide reagent (5 mg/mL; Sigma-Aldrich, St. Louis, MO, USA) was added to each well. After 4 h of incubation, the medium in each well was replaced with 100 μL dimethyl sulfoxide (Sigma-Aldrich). A microplate reader (SpectraMax M5; Molecular Devices) was used to record the absorbance at 490 nm.
Western Blot

The cells were collected in a 1.5-mL centrifuge tube and centrifuged at 3,000 rpm for 10 min, after which the supernatant was discarded. An appropriate amount of the prepared protein lysis buffer (1 mL lysis buffer, 10 μL protease inhibitor, 10 μL phosphatase inhibitor, and 10 μL phenylmethylsulfonyl fluoride) was added to the pellet, and the mixture was shaken vigorously and left on ice for 30 s for 5 min and repeated five times. Centrifuge at 12,000 g for 15 min at 4°C and the supernatant (protein lysate) was collected. Protein concentration was measured using a bicinchoninic acid protein quantification kit following the manufacturer’s instructions. The protein samples were treated with sample buffer and heated to denature the protein. The protein samples were loaded onto a sodium dodecyl sulfate-polyacrylamide gel for a run at 80 V for 0.5 h then. The proteins were transferred to a membrane and blocked with 5% bovine serum albumin for 1.5 h at room temperature. The membrane was incubated in a primary antibody solution with shaking at 4°C overnight. After incubation, the membrane was washed with Tris-buffered saline with Tween 20 (TBST) three times for 10 min each and was incubated with the secondary antibody for 1 h at 37°C. The membrane was then washed with TBST three times for 10 min each, and the color developing solution was added dropwise. The gel was imaged using a gel imager.

Reverse Transcription-Quantitative Polymerase Chain Reaction

Total RNA was extracted using the Trizol method according to the manufacturer’s instructions. The purity and concentration of total RNA are measured using a nucleic acid quantifier. Total RNA was reverse transcribed to cDNA using a Takara kit, and the reaction conditions were 37°C for 15 min, 85°C for 5 s, and 4°C. cDNA was stored at −20°C until use. The PCR reaction system was prepared on ice, and the reaction was carried out on the Bio-Rad Real-Time PCR instrument. The amplification procedures were as follows: step 1, 95°C for 2 min, and step 2, 95°C for 20 s, 60°C for 20 s, and 72°C for 20 s, which was repeated 40 times. Three replicate wells were used per sample, and β-actin was used as the internal reference gene. The experiment was repeated three times. The −2ΔΔCt method was used to determine the expression levels of target genes in each group. The primers used are listed in Table 1.

Statistical Analysis

All data were analyzed using SPSS version 22.0. Measurement data are presented as the mean ± standard deviation. For normally distributed data with uniform variance, the difference between two groups was analyzed using a t test, and the difference between multiple groups was analyzed by one-way analysis of variance. Statistical significance was set at p < 0.05.

Results

RVT Inhibits the Toxicity for HepG2.2.15 Cells and Reduces HBV Replication in vitro

We detected the concentration of HBV DNA in the cell supernatant via ELISA and analyzed its toxicity to HepG2.2.15 cells. RVT at 50 μM had little effect on cell proliferation (Fig. 1a) at the same time, RVT in the range of 0–50 μM increased HBV replication in a concentration-

| Table 1. qRT-PCR primers |
|---------------------------|
| **Forward** | **Reverse** |
| LC3-II | 5′-GATGTCCGACTTATCCGAGGC-3′ | 5′-TTGAGGTGTAAGGCCTTCTA-3′ |
| Beclin1 | 5′-AGGAACCTACAGCTCCTAGTT-3′ | 5′-ATTGTCCCTCTCTCTGATT-3′ |
| p62 | 5′-CGGGTACTGATCCCTGTA-3′ | 5′-TTCCCTCTGGGTGCTTCTC-3′ |
| miR-155 | 5′-GGGAUUGUUGUGUUGUUATT-3′ | 5′-UUUGACAGCUACUAUUCCTT-3′ |
| β-Actin | 5′-TGGCACCAGCAACTGGA-3′ | 5′-CTAAGTCAATAGTGGGCTTAGAAGCA-3′ |

Fig. 1. Effect of resveratrol (RVT) on the toxicity for HepG2.2.15 cells. a Half maximal inhibitory rate of RVT on cytotoxicity. b RVT affects the content of hepatitis B virus (HBV) DNA in cells. *p < 0.05 versus control group.
(For legend see next page.)
dependent manner (Fig. 1b). At 50 μM, RVT had the greatest effect on HBV DNA. Therefore, we used 50 μM as the concentration in the following experiments.

**RVT Inhibits HBV Replication by Activating Autophagy**

WB and RT-qPCR were used to detect the expression of autophagy-related proteins. Compared with the HepG2.2.15 group, the protein expression of LC3-II, LC3-I, and Beclin 1 was decreased while that of p62 was increased in the HepG2.2.15 + RVT group. In addition, rapamycin (RAPA; autophagy activator) enhanced the effect of RVT, whereas 3-MA (autophagy inhibitor) partially reversed the enhancement effect of RVT (Fig. 2).

**RVT Inhibits the Toxicity for HepG2.2.2.15 Cells by Activating Autophagy and Reduces HBV Replication**

We performed the cytotoxicity test and the cytotoxicity of RVT to HepG2.2.2.15 and the concentration of HBV DNA in the supernatant of ELISA cells. Compared with the HepG2.2.15 group, the cytotoxicity of the HepG2.2.15 + RVT group was significantly reduced and the serum HBV content was significantly reduced (both \( p < 0.05 \); Fig. 3a, b). In addition, RAPA enhanced this effect of RVT, whereas 3-MA partially reversed the enhancement effect of RVT.

**Expression of miR-155 in HBV-Transfected Cell Lines**

Some studies have shown that miR-155 plays an important role in the process of HBV replication. RT-qPCR showed that miR-155 expression was higher in HepG2.2.15 cells compared with HepG cells \( ( p < 0.05) \). However, the expression of miR-155 in the RVT treatment group was significantly reduced \( ( p < 0.05; \) Fig. 4).

**miR-155 Promotes HBV Replication by Inhibiting Autophagy**

Previous studies have shown that miR-155 is closely related to autophagy. The studies mentioned above have proved that compared with the HepG2.2.15 group, the protein expression of LC3-II, LC3-I, and Beclin 1 in the HepG2.2.15 + RVT group was decreased, while that of

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**Fig. 2.** Effect of RVT on autophagy-related factors LC3-II, LC3-I, Beclin 1, and p62. **a** Changes in the mRNA levels of LC3-II, LC3-I, Beclin 1, and p62. HepG2.2.15: HepG2.2.15 cell group; HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment group; HepG2.2.15 + RVT + RAPA: HepG2.2.15 cells + RVT treatment + RAPA group; HepG2.2.15 + RVT + 3-MA: HepG2.2.15 cells + RVT treatment + 3-MA treatment group. \*\( p < 0.05 \) versus HepG2.2.15 group; \#\( p < 0.05 \) versus HepG2.2.15 + RVT group; &\( p < 0.05 \) versus HepG2.2.15 + RVT + RAPA group.

**Fig. 3.** Effect of inhibiting or enhancing autophagy on the toxicity of RVT in inhibiting HepG2.2.15 cells. **a** Half maximal inhibitory rate of RVT on cytotoxicity. **b** RVT affects the content of HBV DNA in cells. HepG2.2.15: HepG2.2.15 cell group; HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment group; HepG2.2.15 + RVT + RAPA: HepG2.2.15 cells + RVT treatment + RAPA group; HepG2.2.15 + RVT + 3-MA: HepG2.2.15 cells + RVT treatment + 3-MA treatment group. \*\( p < 0.05 \) versus HepG2.2.15 group; \#\( p < 0.05 \) versus HepG2.2.15 + RVT group; &\( p < 0.05 \) versus HepG2.2.15 + RVT + RAPA group.
p62 was increased. Therefore, we designed and transfect-
eda miR-155 overexpression plasmid, low miR-155 ex-
pression plasmid, and corresponding negative control
and detected the expression of autophagy-related pro-
teins by WB and RT-qPCR. Our results showed that the
effect of RVT was reversed by transfection of pmiR-155
but was enhanced by transfection of shmiR-155 ($p < 0.05$, Fig. 5).

RVT Inhibits the Cytotoxicity for HepG2.2.15
Cells and Reduces HBV Replication by Inhibiting
Autophagy Activated by miR-155
We evaluated the toxicity of RVT to HepG2.2.15 cells
and detected the concentration of HBV DNA in cell su-
pernatant via ELISA. The results showed that compared
with the HepG2.2.15 group, the cytotoxicity and the con-
tent of HBV in serum of the HepG2.2.15 + RVT group
was significantly decreased. We found that the effect of
RVT was partially reversed by pmiR-155 but was en-
hanced by shmiR-155 (Fig. 6).

RVT Inhibits the Molecular Mechanism of HBV
Replication by Inhibiting miR-155 from Activating
Autophagy in vivo
To further verify the results in animals, we constructed
an HBV replication mouse model through tail vein injec-
tion of HBV plasmid. Approximately 1 month after injec-
tion, the HBV DNA copy number in the serum was main-
tained at approximately 103 IU/mL, which meets the
standard of an HBV replication mouse model. The mice
were orally gavaged with RVT (100 mg/kg/day) daily for
2 weeks, and compared with the control group, the HBV
DNA in the serum was significantly reduced in the first
and second weeks after administration ($p < 0.05$; Fig. 7).
These findings suggest that RVT is a strong inhibitor of
HBV replication in vivo and in vitro.

Discussion
HBV infection is prevalent worldwide. According to
the WHO report, there are approximately 257 million
chronic HBV infections worldwide [15]. In 2015, approx-
imately 887,000 people died from HBV infection-related
diseases, of which liver cirrhosis and primary HCC ac-
counted for 52% and 38%, respectively [16]. At present,
treatment of patients with HBV infection primarily in-
volves inhibition of HBV replication for a long time [17–
20], reduction of liver cell inflammation and necrosis and
liver fibrous tissue proliferation, delay and reduction of
liver failure, decompensation of liver cirrhosis, HCC, and
the occurrence of other complications, thereby improving
the quality of life of patients and prolonging their sur-
vival [21].

RVT is a polyphenol compound mainly found in P. cuspidatum, grapes, peanuts, and other plants. It has antitumor, anti-inflammatory, antioxidant, and antiatherosclerosis properties and many other pharmacological activities [9]. In recent years, studies have found that RVT exhibits an antiviral effect. It has a certain effect on Epstein-Barr virus [22], herpes simplex virus [23], human

![Fig. 4. miR-155 expression in HBV-transfected cell lines. HepG: HepG cell group; HepG2.2.15: HepG2.2.15 cell group; HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment group; smiR-155HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment + smiR-155 treatment group; snmiR-155HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment + snmiR-155 group; pmiR-155 + HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment + pmiR-155 treatment group; pNmiR-155-HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment + pNmiR-155 group. *$p < 0.05$ versus HepG group; **$p < 0.05$ versus HepG2.2.15.](image)

![Fig. 5. miR-155 promotes HBV replication by inhibiting autophag-
athy. The effect of miR-155 on autophagy-related factors LC3-II,
LC3-I, Beclin 1, and p62. a Changes in the mRNA levels of LC3-II,
LC3-I, Beclin 1, and p62. b, c Changes in the protein expression of
LC3-II, LC3-I, Beclin 1, and p62. HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment group; smiR-155HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment + smiR-155 treatment group; snmiR-155HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment + snmiR-155 group; pmSMIR-155 + HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment + pmSMIR-155 treatment group; pNmiR-155-HepG2.2.15 + RVT: HepG2.2.15 cells + RVT treatment + pNmiR-155 group. *$p < 0.05$ versus smiR-155HepG2.2.15 + RVT group; **$p < 0.05$ versus pNmiR-155-HepG2.2.15 + RVT group. (For figure see next page.)](image)
In this study, we found that RVT inhibited the toxicity for HepG2.2.15 cells in vitro and reduced HBV replication. RAPA (autophagy activator) can enhance this effect of RVT, while 3-MA (autophagy inhibitor) can partially reverse the enhancement effect of RVT. In addition, we found that compared with HepG cells, miR-155 expression in HepG2.2.15 cells was higher but was reduced in the RVT treatment group. By designing a miR-155 overexpression plasmid, low miR-155 expression plasmid, and corresponding negative control, we found that transfection of pmir-155 can partially reverse the effect of RVT, while transfection of shmiR-155 can enhance its effect.

miR-155 is considered to be an emerging inflammatory mediator that plays an important role in infection, antitumor, and immune regulation [25]. A previous study found that the expression level of miR-155 is correlated with the secretion levels of HBsAg and HBeAg in cells. Related studies have found increased miR-155 expression in patients with HBV infection and along with

immunodeficiency virus [13], and enterovirus [24], among others. In this study, we found that RVT inhibited the toxicity for HepG2.2.15 cells in vitro and reduced HBV replication. RAPA (autophagy activator) can enhance this effect of RVT, while 3-MA (autophagy inhibitor) can partially reverse the enhancement effect of RVT. In addition, we found that compared with HepG cells, miR-155 expression in HepG2.2.15 cells was higher but was reduced in the RVT treatment group. By designing a miR-155 overexpression plasmid, low miR-155 expression plasmid, and corresponding negative control, we found that transfection of pmir-155 can partially reverse the effect of RVT, while transfection of shmiR-155 can enhance its effect.

miR-155 overexpression is an increase in HBsAg and HBeAg secretion and HBV DNA copy number [26]. This shows that miR-155 overexpression can significantly increase the expression level of HBV genes and proteins. In addition, Fang et al. [27] demonstrated that knockout of miR-155 in a transgenic mouse model reduced the antigen presentation and costimulation ability of dendritic cells, thereby regulating the differentiation ability of regulatory T cells. This strengthens the cellular immune response and helps clear the virus. Our findings show that compared with HepG cells, miR-155 expression in HepG2.2.15 cells is higher. After treatment with RVT, transfection of pmir-155 can partially reverse the effect of RVT, while transfection of shmiR-155 can enhance the effect of RVT, consistent with the results of previous studies.

Conclusions

Due to the limitation of experimental conditions, our experiment has not yet verified through which pathway RVT interferes with HBV replication. This will be explored in future experiments. Finally, our research results found that RVT inhibits miR-155, activates autophagy, inhibits the toxicity for HepG2.2.15 cells, and reduces HBV replication, thereby providing a new research direction for the treatment of HBV infection.
Statement of Ethics

This study was approved by the Ethics Committee of the Guangzhou Qite Biotechnology Co., Ltd. (approval number: ChiCTR1900123254).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

Peipei Pan and Guangyan Long designed the research and wrote the manuscript. Peipei Pan, Jiahui Li, Wei Lin, and Guangyan Long performed the experiments and analyzed the data.

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Conflict of Interest Statement

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