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Original Article

Synergistic Effect of Acyclovir and Curcumin on Herpes Simplex Virus Type 1

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Abstract

Background and aims: The emergence of drug-resistant viral strains has emphasized the need for natural antiviral compounds with fewer side effects. Curcumin, a natural polyphenol, exhibits antiviral, antioxidant, antitumor, and anti-inflammatory activities. As drug combinations can reduce resistance development and cytotoxicity by lowering effective doses, this study aimed to evaluate the synergistic effect of curcumin combined with acyclovir against herpes simplex virus type 1 (HSV-1) in vitro.

Methods: In this experimental study, the cytotoxicity of curcumin and acyclovir was assessed on VERO cells using the MTT assay. The antiviral activity of curcumin and acyclovir alone, as well as acyclovir combined with the CC10 concentration of curcumin, was evaluated using MTT and $TCID_{50}$ assays, and the 50% inhibitory concentration (IC_{50}) was calculated. Synergistic effects were analyzed by determining viral growth inhibition percentages at various drug concentrations, and the Combination Index (CI) was calculated using CompuSyn software.

Results: The CC_{50} values of acyclovir and curcumin were 537.7 µM and 74.44 µM, respectively. The IC_{50} values were 0.395 µM for acyclovir, 12.6 µM for curcumin, and 0.144 µM for the combination of acyclovir with 20 µM (CC10) curcumin. Both compounds significantly reduced viral titers individually and in combination. The combined treatment demonstrated a synergistic antiviral effect at the tested concentrations.

Conclusion: These findings indicate that curcumin has notable antiviral activity against HSV-1 in vitro and significantly enhances acyclovir's antiviral efficacy through synergistic interaction, suggesting potential for future clinical evaluation.

Keywords: Synergism, Antiviral agents, Curcumin, Acyclovir, Herpes simplex virus type 1

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Introduction

The herpes simplex virus (HSV) belongs to the family *Herpesviridae* and the subfamily *Alphaherpesvirinae*. It is considered one of the most common human pathogenic viruses. *Herpesviridae* represents a large family of DNA viruses that cause a wide range of significant diseases in both adults and children (1). HSV primarily affects the skin and mucous membranes regardless of viral type. Primary exposure to HSV leads to viral invasion of epithelial cells, followed by intracellular replication at the site of infection. Viral attachment and entry into host cells occur through interactions between viral glycoproteins and host cell membrane receptors. These viruses cause a broad spectrum of illnesses, ranging from mild to severe, including oral herpes, genital herpes, herpetic encephalitis, recurrent miscarriage, and meningitis. In immunocompromised individuals and newborns, HSV often leads to painful and debilitating lesions, and in the worst cases, death (2, 3). Given the limitations of most antiviral drugs, the development of new antiviral agents or the use of drug combinations is of great importance. Drug combinations reduce the likelihood of mutant, drug-resistant viruses emerging and also decrease cytotoxicity by requiring lower concentrations of each drug.

Curcumin is a natural polyphenol derived from the plant *Curcuma longa*. This biomolecule is a symmetrical

compound consisting of two 4-hydroxy-3-methoxyphenyl rings linked by α, β-unsaturated carbonyl groups. Curcumin is a crystalline compound with a bright orange-yellow color that exhibits significant pharmacological effects both *in vitro* and *in vivo* through various mechanisms. It is also used as food and a natural coloring agent. Curcumin is a tautomeric compound that exists in the keto form in water and the enol form in organic solvents (4-7). Curcumin possesses various properties, including antiviral, anti-inflammatory, antioxidant, antibacterial, anti-arthritic, analgesic, antiparasitic, antimalarial, antidepressant, antidiabetic, anticancer, anti-obesity, anti-asthmatic, wound healing, and neuroprotective activities (5). Many studies have reported the antiviral effects of curcumin and its derivatives against a variety of viruses, such as herpesviruses, adenoviruses, hepatitis viruses, and influenza viruses, under laboratory conditions (6, 8-14). Research suggests that curcumin likely inhibits HSV-1 by interfering with the recruitment of RNA polymerase II at the promoters of immediate early (IE) genes. This inhibition occurs through curcumin's effect on viral mediator protein VP16 required for RNA polymerase II recruitment, independent of the histone acetyltransferase activity of transcriptional coactivators p300/CBP (11). Other studies have shown that curcumin suppresses replication of human cytomegalovirus by downregulating heat shock protein 90 (Hsp90), which is essential for IE gene expression during viral pathogenesis (13).

Combination drug therapy is an effective strategy for managing various diseases, as it can improve treatment outcomes and reduce the development of drug resistance. In chronic conditions such as cancer, diabetes, and cardiovascular diseases, combining agents with different mechanisms of action has been shown to enhance therapeutic efficacy while minimizing cytotoxicity through the use of lower drug concentrations (15-17). Given that curcumin and acyclovir (ACV) act through distinct antiviral mechanisms, their combination may provide a synergistic effect against HSV infections. The present study was designed to investigate the synergistic effect of curcumin in combination with acyclovir against HSV-1 infection under laboratory conditions.

Materials and Methods

Cells and Viruses

Vero cells, obtained from the Cell Bank of the Pasteur Institute of Iran, were used for HSV-1 propagation. The cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% Fetal Bovine Serum (FBS; Gibco, USA) and 1% Pen/Strep (Gibco, USA) at 370C in a 5% CO2 atmosphere and humidified incubator. The same medium containing 2 % PBS was used for cytotoxicity and antiviral assays. HSV-1 (HSV-1, KOS strain) was provided by the Virology Laboratory of the Basic Health Sciences Institute, Shahrekord University of Medical Sciences (Shahrekord, Iran). Virus stock was prepared by infecting confluent monolayer Vero cells in 75 cm2 culture flasks using DMEM medium with 2 % FBS at 37 °C with 5 % CO2. Virus titer was determined by the cytopathic effect (CPE) of HSV-1 on Vero cells and expressed as the 50% tissue culture infective dose (TCID50)/mL. The infective titer of the stock solution was 106/7TCID50/mL. Aciclovir (9-(2-hydroxyethoxymethyl) (Sigma, USA) and curcumin (Sigma, USA) were dissolved in dimethyl sulfoxide (DMSO; Samchun, Korea) and phosphate-buffered saline (PBS) to obtain a completely homogeneous solution. The final DMSO concentration in the cell culture did not exceed 0.02%

Cytotoxicity Assay

Before assessing antiviral activity, the cytotoxicity of the compounds on Vero cells was evaluated in the absence of the virus to determine their non-toxic concentrations. For this purpose, in 96-well plates containing a cell monolayer, after removing the culture medium and washing the cells with PBS buffer, serial dilutions of the compounds were prepared in DMEM supplemented with 2% FBS, added to the wells, and incubated at 37 °C with 5% CO_2 for 48 hours. Cell viability was then assessed using the MTT colorimetric assay, performed in triplicate for each compound. The 50% cytotoxic concentration (CC_{50}) was calculated from the dose–response curve using regression analysis in GraphPad software (18, 19).

Evaluation of Antiviral Activity Using MTT Assay

Antiviral activity was assessed using the MTT assay. After the formation of a confluent monolayer in 96-well microplates, the culture medium was removed, and 100 µL of medium containing non-toxic concentrations of acyclovir (1, 0.5, 0.25, 0.125, 0.06, 0.03 µM), curcumin (100,30.10.3,1 µM), and their combination (curcumin at CC_{10} concentration (20 µM) combined with various concentrations of acyclovir), with 100 $TCID_{50}$ of HSV-1 were added to each well. The plates were then incubated at 37 °C with 5% CO_2 for 72 hours. Following incubation, the MTT assay was performed as described previously, and the viral inhibition rate was calculated. After three independent repetitions, the 50% inhibitory concentration (IC_{50}) was determined as the minimum concentration of the compound required to inhibit 50% of viral replication, using regression analysis. Appropriate controls were included in each assay: a negative control (cells without virus or compounds), a virus control (virus without compounds), and a positive drug control (acyclovir). The selectivity index (SI), used to evaluate a compound's potential as a drug candidate, was calculated as the ratio of CC_{50} to IC_{50}. The procedure was carried out in triplicate.

Evaluation of Antiviral Effect Using $TCID_{50}$ Assay

Antiviral activity was also evaluated using the $TCID_{50}$ method. After the formation of a cell monolayer in 48-well microplates, 200 µl of medium containing non-toxic concentrations (below CC_{50}) of acyclovir, curcumin, their combination, and 100 $TCID_{50}$ of herpes virus were

added to each well. The plates were incubated for 48 h at 37 °C with 5% CO_2, after which the supernatant was collected, and the viral titer of each well was calculated by the $TCID_{50}$ method. For this, Vero cells were cultured in 96-well microplates. After forming a cell monolayer, serial 10-fold dilutions of the virus in medium containing 2% FBS were added to the wells. The microplates were incubated at 37°C with 5% CO_2 until cytopathic effects (CPE) appeared. The results were collected, and the viral titer ($TCID_{50}$) was calculated using the Reed–Muench method (20), performed in triplicate for each compound.

Evaluation of Synergistic Effect Using Compusyn Software

To evaluate potential synergy, the HSV-1 virus was treated with various concentrations of acyclovir and curcumin, alone and in combination, for 48 h, and the percentage of viral growth inhibition was assessed. The combination index (CI) values were calculated using CompoSyn 1.0 software (www.combosyn.com). The CI test was carried out in triplicate (n = 3), and the Combination Index (CI) was calculated. The CI value interprets the drug interaction as: synergy (CI < 1), additivity (CI = 1), or antagonism (CI > 1).

Data Analysis Method

Data were analyzed using SPSS 25 and GraphPad software. The effects of different compound concentrations on the cell line were compared with those of the negative control. Probit regression analysis was used to calculate CC_{50} and IC_{50} values. Compusyn software was employed to assess the drug combination index.

Results

Cytotoxic Effects of the Compounds Using the MTT Assay

According to the probit test results, there was a significant difference among the study groups in the percentage of VERO cell death ($P < 0.05$; Figure 1). The rate of cell death increased with increasing compound concentrations. The CC_{50} values for acyclovir and curcumin were 537.7 µM (95% CI: 448.7–705.7) and 74.44 µM (95% CI: 62.6–89.6), respectively.

Evaluation of Antiviral Activity

Based on the results, the IC_{50} values in acyclovir, curcumin, and curcumin at CC_{10} concentration (20 µM) combined with various concentrations of acyclovir were 0.395 (95% CI: 0.305–0.519) µM, 12.6 (95% CI: 8.85–18.3) µM, and 0.144 (95% CI: 0.119–0.175) µM, respectively (Figure 2).

The findings of this study demonstrated that the herbal compound curcumin, with a selectivity index (SI) of 13.2, possesses good antiviral potential against HSV-1 *in vitro*. Moreover, the addition of curcumin at 20 µM (CC_{10})

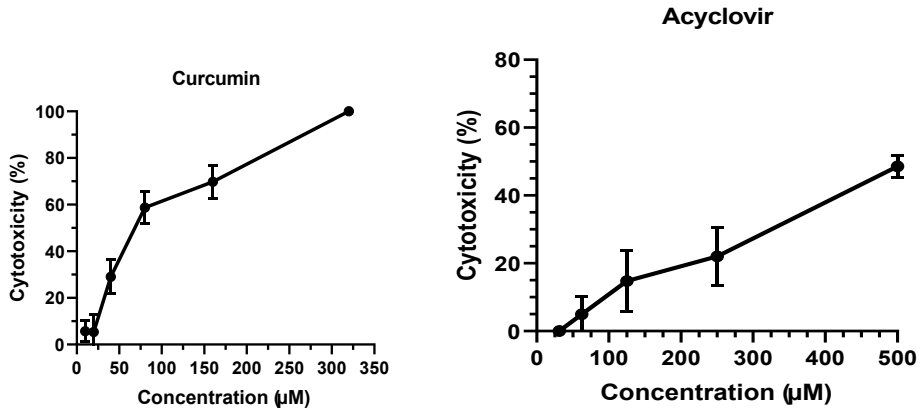

Figure 1. The cytotoxicity effect of acyclovir and curcumin in VERO cells. The death rate was calculated using the MTT assay. The values are expressed as the means ± standard deviations of two independent experiments performed in triplicate.

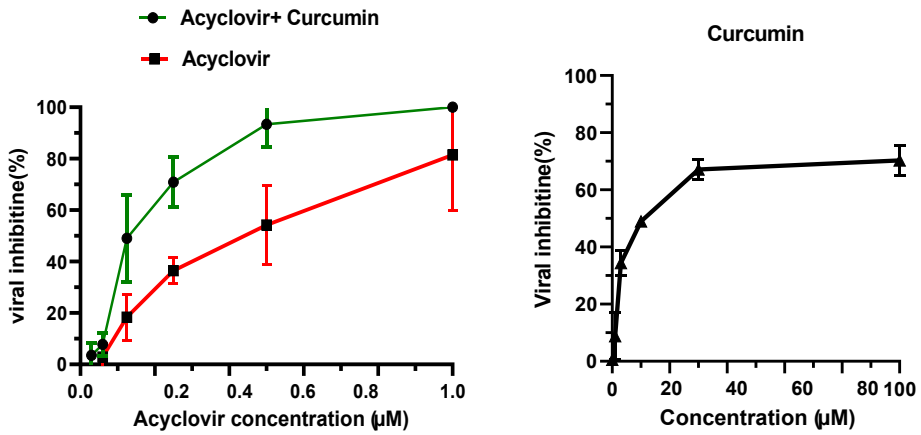

Figure 2. Anti-herpes simplex virus activity of curcumin, acyclovir, and their combination using MTT assay

in combination reduced the effective concentration of acyclovir by approximately threefold.

For the combination experiments, curcumin at its CC_{10} concentration (20 µM) was combined with various concentrations of acyclovir; the values are expressed as the means ± standard deviations of two independent experiments performed in triplicate.

Effect of Curcumin and Acyclovir on Viral Titer

The effect of curcumin, acyclovir, and their combination on viral titer was evaluated using the $TCID_{50}$ assay. The results showed that both acyclovir and curcumin alone significantly reduced viral titer ($P < 0.05$, Figure 3). Furthermore, simultaneous treatment with acyclovir and curcumin resulted in a substantially greater reduction in viral titer than acyclovir alone ($P < 0.05$; Figure 4).

Evaluation of Synergistic Effect Using Compusyn Software

The synergistic effect of acyclovir and curcumin was analyzed using Compusyn software. The percentage of viral growth inhibition at different concentrations of each compound alone and in combination was assessed, and the Combination Index (CI) was calculated.

In this study, acyclovir was tested at concentrations ranging from 0.03 to 1 µM, and curcumin at concentrations from 1 to 30 µM. The results demonstrated that co-administration of acyclovir and curcumin produced a synergistic effect. The strongest synergy was observed at 0.1 µM acyclovir combined with 3 µM curcumin, yielding a CI of 0.438. Overall, curcumin and acyclovir exhibited a synergistic relationship in their anti–HSV-1 activity (Table 1).

Discussion

In the present study, the antiviral effects of curcumin and acyclovir were evaluated against HSV-1 using MTT and $TCID_{50}$ assays. The results demonstrated that the curcumin, with a selectivity index (SI) of 5.9, has significant antiviral potential against HSV-1 *in vitro*. These findings are consistent with previous studies reporting the antiviral activity of curcumin and its derivatives against various viruses, including herpesviruses, adenoviruses, hepatitis viruses, and influenza viruses *in vitro* (8-10, 12, 13). Research suggests that curcumin likely inhibits HSV-1 by interfering with the recruitment of RNA polymerase II at the promoters of immediate early (IE) genes. This inhibition occurs through curcumin's effect on viral mediator protein VP16 required for RNA polymerase II recruitment, independent of the histone acetyltransferase activity of transcriptional coactivators p300/CBP (11). Other studies have shown that curcumin suppresses replication of human cytomegalovirus by downregulating heat shock protein 90 (Hsp90), which is essential for IE gene expression during viral pathogenesis (13). El-

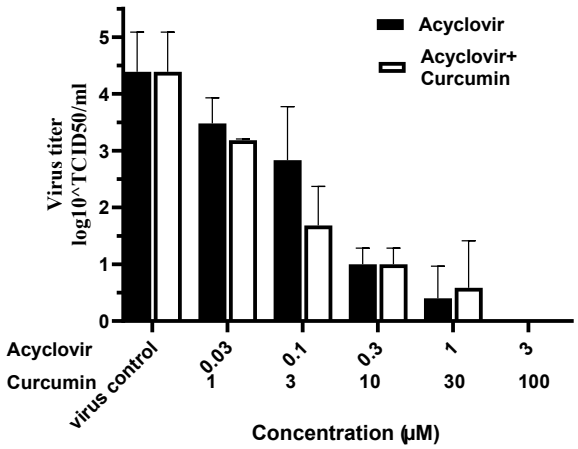

Figure 4. Comparison of viral titer at different concentrations of acyclovir alone and in combination with curcumin based on the $TCID_{50}$ assay. For the combination experiments, curcumin at its CC_{10} concentration (20 µM) was combined with acyclovir at various concentrations. The values are expressed as the means ± standard deviations of three independent experiments.

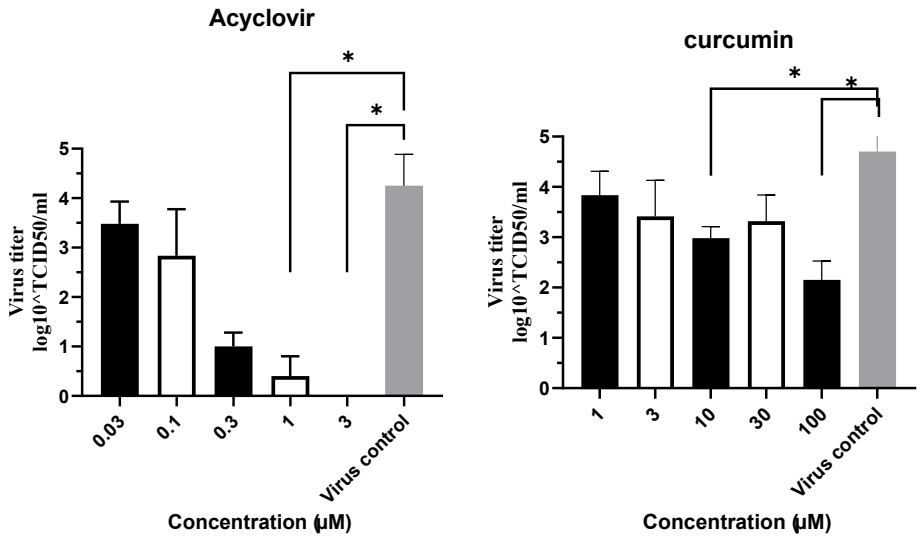

Figure 3. Comparison of viral titer at different concentrations of curcumin and acyclovir based on the $TCID_{50}$ assay. The significance of the results was evaluated using the nonparametric Kruskal-Wallis and post hoc Dunn's multiple comparisons tests. The values are expressed as the means ± standard deviations of three independent experiments; *$P < 0.05$

Table 1. Combination index (CI) values for different concentrations of curcumin and acyclovir against HSV-1

Description	CI	Curcumin (μM)	Acyclovir (μM)
antagonism	2.6	30	1
antagonism	1.3	10	0.3
synergism	0.438	3	0.1
synergism	0.67	1	0.03

The synergistic effect was evaluated using CompuSyn software. The Combination Index (CI) theorem interprets the drug interaction as synergy (CI < 1), additivity (CI = 1), or antagonism (CI > 1). The antiviral effect was measured using the MTT assay. CI:

Halim et al examined the antiviral activity of curcumin-loaded proniosomal gel against HSV-1 *in vitro* and in silico, reporting that such formulations could serve as an effective topical delivery system for HSV-1 treatment (21). The possible molecular synergy between curcumin and acyclovir may arise from their different mechanisms of action. While acyclovir targets the final step of viral replication by inhibiting viral DNA polymerase activity, curcumin interferes with early transcriptional events. It modulates host signaling pathways, such as NF-κB and MAPK, thereby leading to more comprehensive suppression of HSV-1 replication and reduced viral gene expression.

In this study, the addition of 20 μM curcumin (CC_{10}) reduced the effective concentration of acyclovir by approximately threefold. Co-administration of acyclovir and curcumin also produced a significant reduction in viral titer compared to acyclovir alone, demonstrating synergistic antiviral effects at the tested concentrations. Due to its broad biological properties, curcumin is frequently combined with other drugs, particularly chemotherapeutic agents, to enhance therapeutic effects and reduce side effects. Jalal Abadi et al reported that curcumin enhances the antitumor effects of cisplatin while mitigating its side effects (22). When two or more drugs interact, the combined effect can exceed the sum of individual effects, resulting in synergy. Such synergistic combinations offer significant therapeutic advantages over monotherapy (23). Previous studies have shown that acyclovir synergizes with other drugs, improving efficacy and reducing viral resistance (24, 25). For instance, Quenelle et al reported that the combination of acyclovir and pritelivir (a helicase–primase inhibitor) exhibits potent antiviral activity against HSV-1 and HSV-2 infections, including herpes simplex encephalitis (25). Gong et al demonstrated that a combination of acyclovir and betulin, a pentacyclic triterpenoid, is more effective against HSV-1 and HSV-2 infections than either agent alone (26). Such drug combinations reduce the likelihood of resistant viral strains and lower cytotoxicity by enabling lower drug concentrations.

Considering our results and previous studies, curcumin exhibits antiviral activity against HSV-1 through mechanisms distinct from acyclovir. Additionally, multiple reports indicate that curcumin promotes wound healing, suggesting that combining curcumin with acyclovir could improve the efficacy of HSV treatment.

This study has certain limitations that should be acknowledged. First, curcumin exhibits low oral bioavailability and limited systemic distribution; therefore, the concentrations used in in vitro experiments may not be achievable in vivo unless advanced delivery systems, such as nanoparticle-based formulations, are employed. Second, since acyclovir-resistant HSV-1 strains were not examined in this study, further research is needed to determine whether the curcumin–acyclovir combination is effective against resistant viral strains.

Conclusion

The results of this study demonstrate that the herbal compound curcumin possesses significant antiviral potential against HSV-1 *in vitro*. Co-administration of curcumin with acyclovir significantly reduces the required dose of acyclovir. Our findings, for the first time, show that low doses of acyclovir combined with curcumin exert a synergistic effect on HSV replication *in vitro*. This combination may enhance the therapeutic efficacy of acyclovir in the treatment of HSV infections.

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Authors' Contribution

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Competing Interests

The authors declare no conflict of interest.

Ethical Approval

Ethical considerations in this study included obtaining permission from the Ethics Committee of Shahrekord University of Medical Sciences (Ethical Code IR.SKUMS.MED.REC.1402.028).

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