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Original Article

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

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Abstract

Introduction: 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. Considering that drug combinations can reduce resistance development and cytotoxicity by lowering effective doses, this study aimed to evaluate the synergistic effects 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 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Moreover, the antiviral activity of curcumin and acyclovir alone, as well as acyclovir combined with the 10% cytotoxic concentration (CC10) of curcumin, was evaluated using MTT and 50% tissue culture infective dose assays, and the 50% inhibitory concentration (IC50) underwent calculation. Ultimately, synergistic effects were analyzed by determining viral growth inhibition percentages at various drug concentrations, and the combination index was computed using CompuSyn 1.0.

Results: The CC50 values of acyclovir and curcumin were 537.7 µM and 74.44 µM, respectively. Furthermore, the IC50 values were 0.395, 12.6 µM, and 0.144 µM for acyclovir, curcumin, and the combination of acyclovir with 20 µM (CC10) curcumin, respectively. Both compounds significantly reduced viral titers individually and in combination. Finally, the combined treatment demonstrated a synergistic antiviral effect at the tested concentrations.

Conclusion: Overall, curcumin had notable antiviral activity against HSV-1 in vitro and substantially enhanced acyclovir's antiviral efficacy through synergistic interaction, suggesting potential for future clinical evaluations.

Keywords: Synergism, Antiviral Agents, Curcumin, Acyclovir, Herpes Simplex Virus Type 1

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Introduction

The herpes simplex virus (HSV), which belongs to the family *Herpesviridae* and the subfamily *Alphaherpesvirinae*, is considered one of the most common human pathogenic viruses. *Herpesviridae* represents a large family of DNA viruses that cause a wide range of serious diseases in both adults and children (1). HSV primarily affects the skin and mucous membranes regardless of the viral type. Primary exposure to HSV leads to the 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. In addition, 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 frequently 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. It should be noted that drug combinations reduce the likelihood of the emerging mutant, drug-resistant viruses and decrease cytotoxicity by requiring lower concentrations of each drug.

Curcumin is a natural polyphenol that is derived from the plant *Curcuma longa*. This biomolecule is a symmetrical compound consisting of two 4-hydroxy-3-

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methoxyphenol rings linked by α, β-unsaturated carbonyl groups. Moreover, 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. In addition, it is used as food and a natural coloring agent. Additionally, curcumin is a tautomeric compound that exists in the keto form in water and the enol form in organic solvents (4-7). This compound 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). Furthermore, 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 ribonucleic acid (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 and CBP (11). Likewise, curcumin suppresses the replication of human cytomegalovirus by downregulating heat shock protein 90, 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 while reducing the development of drug resistance. In chronic conditions (e.g., 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 have a synergistic effect against HSV infections. Therefore, th present study has been designed to investigate the synergistic effect of curcumin in combination with ACV 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's medium (DMEM) supplemented with 10% fetal bovine serum (FBS; Gibco, USA) and 1% Pen/Strep (Gibco, USA) at 37°C in a 5% CO_2 atmosphere and humidified incubator. The same medium containing 2 % phosphate-buffered saline (PBS) was employed 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). Moreover, virus stock was prepared by infecting confluent monolayer Vero cells in 75 cm^2 culture flasks using DMEM with 2% FBS at 37°C with 5% CO_2. In addition, virus titer was determined by the cytopathic effect of HSV-1 on Vero cells and expressed as the 50% tissue culture infective dose ($TCID_{50}$)/mL. The infective titer of the stock solution was10^6/7 $TCID_{50}$/mL. Further, acyclovir (9-(2-hydroxyethoxymethyl; Sigma, USA) and curcumin (Sigma, USA) were dissolved in dimethyl sulfoxide (Samchun, Korea) and PBS to obtain a completely homogeneous solution. The final dimethyl sulfoxide 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, the serial dilutions of the compounds were prepared in DMEM supplemented with 2% FBS, added to the wells, and finally incubated at 37°C with 5% CO_2 for 48 hours. Cell viability was then assessed using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay, performed in triplicate for each compound. Furthermore, the 50% cytotoxic concentration and the 10% cytotoxic concentration were calculated from the dose-response curve by regression analysis using GraphPad software, version 9.0.0 (18, 19). Ultimately, the 10% cytotoxic concentration was considered the maximum non-toxic concentration for antiviral assays in the combination therapy of curcumin and ACV (18).

Evaluation of Antiviral Activity Using 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide 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 the medium containing the non-toxic concentrations of ACV (1 µM, 0.5 µM, 0.25 µM, 0.125 µM, 0.06 µM, 0.03 µM), curcumin (100, µM 30.10.3 µM, 1 µM), and their combination (curcumin at the CC_{10} concentration [20 µM], combined with various concentrations of ACV), with 100 $TCID_{50}$ of HSV-1 were added to each well. Subsequently, the plates were 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. Moreover, 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 (ACV).

Eventually, the selectivity index (SI), used to evaluate a compound's potential as a drug candidate, was computed as the ratio of CC_{50} to IC_{50}. The procedure was conducted in triplicate.

Evaluation of Antiviral Effects Using 50% Tissue Culture Infective Dose Assay

Antiviral activity was evaluated using the $TCID_{50}$ method. After the formation of a cell monolayer in 48-well microplates, 200 µL of the medium containing the non-toxic concentrations (below CC_{50}) of ACV, curcumin, their combination, and 100 $TCID_{50}$ of the herpes virus were added to each well. The plates were incubated for 48 hours 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. In addition, Vero cells were cultured in 96-well microplates. After forming a cell monolayer, serial 10-fold dilutions of the virus in the medium containing 2% FBS were added to the wells. The microplates were incubated at 37°C with 5% CO_2 until cytopathic effects appeared. The results were collected, and the viral titer ($TCID_{50}$) was measured using the Reed–Muench method (20), performed in triplicate for each compound.

Evaluation of Synergistic Effects Using CompuSyn Software

To evaluate potential synergy, the HSV-1 virus was treated with various concentrations of ACV and curcumin, alone and in combination, for 48 hours, and the percentage of viral growth inhibition was assessed. The combination index (CI) values were computed using CompuSyn 1.0 software (www.combosyn.com). The CI test was performed in triplicate (n = 3), and the 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 (version 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 estimate CC_{50} and IC_{50} values. Finally, CompuSyn software was employed to assess the drug CI.

Results

Cytotoxic Effects of the Compounds Using the 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide 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

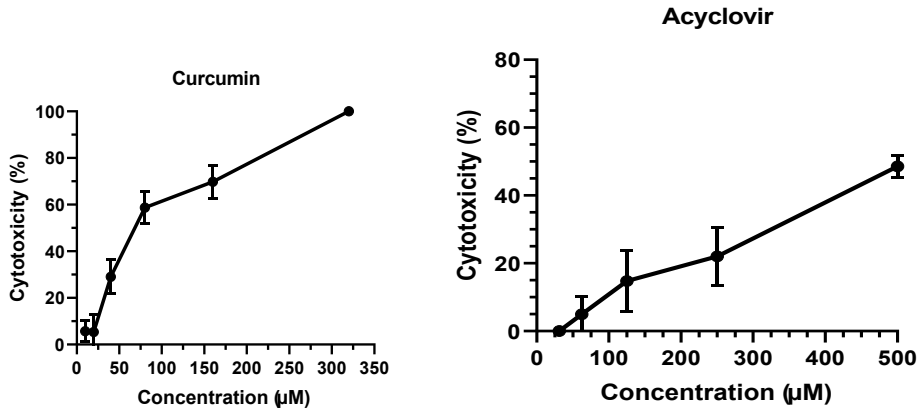


Figure 1. The Cytotoxicity Effect of Acyclovir and Curcumin in VERO Cells
Note. MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. The death rate was calculated using the MTT assay. The values are expressed as the means ± standard deviations of two independent experiments performed in triplicate.

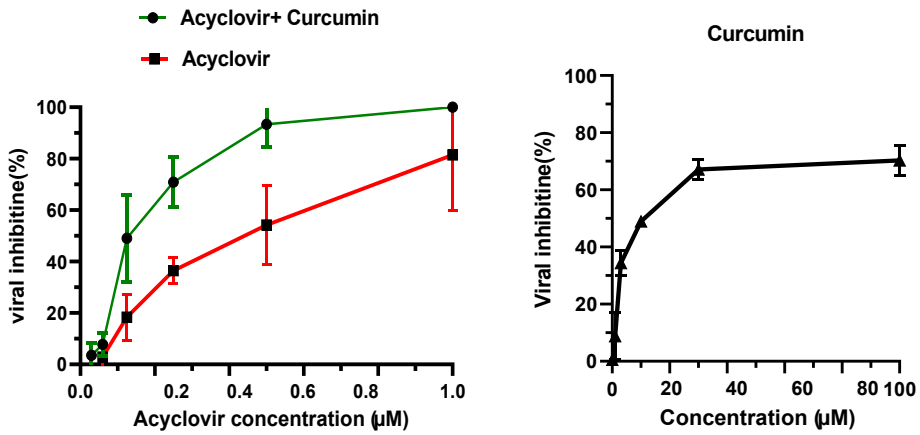


Figure 2. Anti-Herpes Simplex Virus Activity of Curcumin, Acyclovir, and Their Combination Using MTT Assay
Note. MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

increased with increasing compound concentrations. Further, the CC_{50} values for ACV and curcumin were 537.7 μM (95% confidence interval: 448.7–705.7) and 74.44 μM (95% confidence interval: 62.6–89.6), respectively.

Evaluation of Antiviral Activity

Based on the results, the IC_{50} values in ACV, curcumin, and curcumin at the CC_{10} concentration (20 μM) combined with various concentrations of ACV were 0.395 μM (95% confidence interval: 0.305–0.519), 12.6 μM (95% confidence interval: 8.85–18.3), and 0.144 μM (95% confidence interval: 0.119–0.175), respectively (Figure 2). The findings of this study demonstrated that the herbal compound curcumin, with an SI of 13.2, possesses acceptable antiviral potential against HSV-1 *in vitro*. Moreover, the addition of curcumin at 20 μM (CC_{10}) in combination reduced the effective concentration of ACV by approximately threefold.

For the combination experiments, curcumin at its CC_{10} concentration (20 μM) was combined with various concentrations of ACV; 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, ACV, and their combination on viral titer was evaluated using the $TCID_{50}$ assay. The results revealed that both ACV and curcumin alone significantly reduced viral titer ($P < 0.05$, Figure 3). Furthermore, simultaneous treatment with ACV and curcumin resulted in a substantially greater decrease in viral titer than ACV alone ($P < 0.05$, Figure 4).

Evaluation of Synergistic Effects Using CompuSyn Software

The synergistic effect of ACV 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 CI was calculated.

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

Discussion

In the present study, the antiviral effects of curcumin and ACV were evaluated against HSV-1 using MTT and

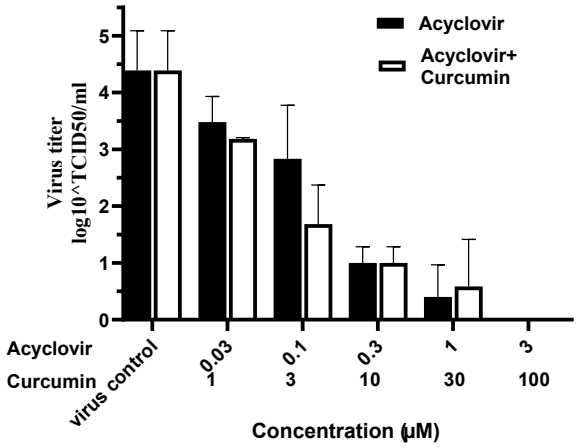


Figure 4. Comparison of Viral Titer at Different Concentrations of Acyclovir Alone and in Combination With Curcumin Based on the TCID50 Assay
Note. TCID50: 50% tissue culture infective dose; CC10: The 10% cytotoxic concentration. For the combination experiments, curcumin at its CC concentration (20 μM) was combined with acyclovir at various concentrations. The values are shown as the means ± standard deviations of three independent experiments.

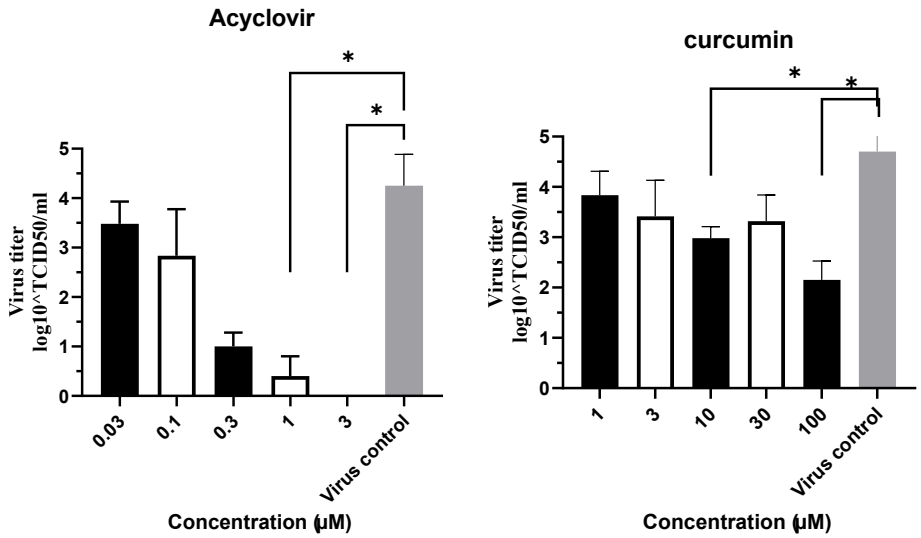


Figure 3. Comparison of Viral Titer at Different Concentrations of Curcumin and Acyclovir Based on the TCID50 Assay
Note. TCID50: 50% tissue culture infective dose. The significance of the results was evaluated using the nonparametric Kruskal-Wallis and post hoc Dunn's multiple comparisons tests. The values are demonstrated as the means ± standard deviations of three independent experiments; *$P < 0.05$.

Table 1. Combination Index Values for Different Concentrations of Curcumin and Acyclovir Against HSV-1

Acyclovir (μM)	Curcumin (μM)	Combination Index	Description
1	30	2.6	Antagonism
0.3	10	1.3	Antagonism
0.1	3	0.438	Synergism
0.03	1	0.67	Synergism

Note. HSV: Herpes simplex virus; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; CI: Combination index. The synergistic effect was evaluated using CompuSyn software. The combination index 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.

$TCID_{50}$ assays. Based on the results, the curcumin, with an SI of 5.9, had significant antiviral potential against HSV-1 *in vitro*. These findings are consistent with those of 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). According to research curcumin probably inhibits HSV-1 via interfering with the recruitment of RNA polymerase II at the promoters of IE genes. Such inhibition happens by the effect of curcumin on viral mediator protein VP16 necessary for RNA polymerase II recruitment, independent of the histone acetyltransferase activity of transcriptional coactivators CBP and p300 (11). Similarly, curcumin suppresses replication of human cytomegalovirus through downregulating heat shock protein 90, which is vital for the expression of IE genes during viral pathogenesis (13). El-Halim et al examined the antiviral activity of the curcumin-loaded proniosomal gel against HSV-1 *in vitro* and *in silico*, demonstrating that such formulations can serve as an effective topical delivery system for HSV-1 treatment (21). The possible molecular synergy between curcumin and ACV may arise from their different mechanisms of action. While ACV 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 nuclear factor-kappa B and mitogen-activated protein kinase, 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 ACV by approximately threefold. Moreover, the co-administration of ACV and curcumin produced a sharp decline in the viral titer compared to ACV alone, confirming 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 while reducing side effects. Jalal Abadi et al found 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 ACV synergizes with other drugs, improving efficacy while decreasing viral resistance (24, 25). For instance, Quenelle et al reported that the combination of ACV and pritelivir (a helicase-primase inhibitor) exhibits potent antiviral activities against HSV-1 and HSV-2 infections, including herpes simplex encephalitis (25). Similarly, Gong et al demonstrated that a combination of ACV 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 those of previous studies, curcumin represents antiviral activities against HSV-1 through mechanisms distinct from ACV. Additionally, multiple reports indicate that curcumin promotes wound healing, suggesting that combining curcumin with ACV can improve the efficacy of HSV treatment.

This study had certain limitations. 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. In addition, ACV-resistant HSV-1 strains were not examined in this study. Accordingly, further research is needed to determine whether the curcumin-ACV combination is effective against resistant viral strains.

Conclusion

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

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Authors' Contribution

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Writing–Original Draft: Maryam Reisi, Dhiya Altememy, Pegah Khosravian, Mohammad-Taghi Moradi.
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Competing Interests

The authors declare no conflict of interests.

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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