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Evaluating Nanocurcumin's Influence on Human Papillomavirus Clearance and Cervical Smear Diagnostic Accuracy in High-Risk HPV Patients: A Randomized Clinical Trial

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Abstract

Objectives: Human papilloma virus (HPV) is the primary cause of cervical cancer, and its prevention is crucial in reducing the risk of developing this cancer. To explore potential preventive measures, we conducted a double-blind randomized clinical trial aiming at investigating the impact of oral nanocurcumin on HPV infection clearance in women who had high-risk results from HPV genotyping.

Materials and Methods: We enrolled women with high-risk HPV test results as participants in this study. Through a random assignment process, the participants were divided into two groups: one group received oral nanocurcumin (80 mg/d) along with standard treatment, while the other group received a placebo and standard treatment. The duration of the treatment period was 4 months. HPV clearance was the primary outcome measure, and we also closely monitored and recorded any adverse effects experienced by the patients as the secondary outcome.

Results: In the intervention group, we observed an HPV clearance rate of 75.0%, compared to 42.8% in the placebo group. This difference was statistically significant, with a P value of 0.026, indicating a beneficial effect of oral nanocurcumin in promoting HPV clearance. For specific HPV subtype 16, the clearance rate was higher in the nanocurcumin intervention group (71.4%) compared to the placebo group (50.0%). Similarly, for HPV subtype 18, the nanocurcumin intervention group showed a clearance rate of 77.8%, while the placebo group had a clearance rate of 37.5%. Although the sub-group analysis did not yield statistically significant differences ($P > 0.05$), the observed difference indicated a potential beneficial effect of nanocurcumin.

Conclusions: Our study suggests that oral nanocurcumin has the potential to enhance HPV infection clearance. Furthermore, the treatment with oral nanocurcumin appears to be safe, as we observed minimal major adverse events reported during the study period.

Keywords: Cervical cancer, Human papilloma virus (HPV), Clearance, Nanocurcumin

Introduction

Cervical cancer is a significant health concern, especially for women of reproductive age. According to GLOBOCAN 2020 data, there were over 600 000 new cases of cervical cancer diagnosed worldwide in 2020, resulting in 341,831 deaths, with a majority occurring in low- and middle-income countries (1). In Iran, cervical cancer is a growing public health challenge, with an estimated incidence rate of 2.9 per 100 000. The good news is that 100% of cervical cancer cases could be prevented through human papilloma virus (HPV) prevention and treatment (2).

HPV is a self-limiting infection, with over 90% of cases resolving without any treatment (3). However, certain HPV subtypes, particularly 16 and 18, are known to cause cervical cancer, as classified by the World Health Organization's International Agency for Research on Cancer (WHO-IARC) monograph due to sufficient evidence supporting their role as carcinogens for humans (4).

Cervical cancer is preventable, and various primary and secondary preventive approaches, such as HPV vaccination and Pap smear screening tests, have been developed over the years (5). Pap smears and HPV testing are recommended approaches for women aged 30-65 years, providing valuable information to clinicians about cervical cancer prediction, infections, precancerous changes, and early-stage cervical cancer detection (6).

While there have been significant advancements in cervical cancer treatment, survival, and early diagnosis (7,8), there is still limited evidence regarding the treatment of HPV infection, which is the main cause of cervical cancer development. Effective therapeutic interventions

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Key Messages

- Due to the prevalence of HPV and its risk in women, as it is the main cause of cervical cancer, there is currently no definitive treatment for HPV. However, there is a pressing need for further research in this area to find ways to help manage and eliminate this risk factor more effectively.
- According to previous studies, nanocurcumin with high absorption properties, as well as immune system and anti-inflammatory properties, has been considered for evaluating its efficacy in the treatment of high-risk HPV. However, no studies have so far investigated the use of oral nanocurcumin for this treatment.

to clear HPV infection could significantly reduce the risk of developing cervical cancer. Unfortunately, no effective and safe treatment for HPV clearance currently exists. Some experimental in-vitro studies have shown promising outcomes with herbal products like curcumin. Curcumin, a molecular compound, exhibits remarkable pleiotropic or multifaceted properties, manifesting a wide range of therapeutic effects. These multifaceted effects arise from curcumin's ability to interact with various molecules and regulate multiple pathways and molecular targets (9). Previous research has revealed that curcumin directly interacts with over 30 different proteins, including DNA polymerase, thioredoxin reductase, protein kinase, tubulin, and lipoxygenase (10,11). Moreover, curcumin plays a role in modulating cell-to-cell signaling cascades, which are critical for efficient viral replication. It achieves this by attenuating signaling pathways like NF-κB and PI3K/Akt. Furthermore, curcumin impacts cellular post-transcriptional and post-translational modifications, which hinder viral replication at various stages, including genome replication and viral attachment (10,11). Studies have shown that curcumin can prevent the development of cervical cancer caused by the papillomavirus by inhibiting the transfer of NF-κB into the nucleus, reducing the expression of oncogenes related to HPV, and inducing apoptosis in HPV-infected cells. Other mechanisms contributing to curcumin's anti-cancer properties include the suppression of HPV oncoproteins and the upregulation of tumor suppressor genes such as P53 (12). In a study conducted in India, creams and capsules containing curcumin were employed to treat 287 women with HPV. The results demonstrated that the virus was eradicated in over 19% of cases, and these women experienced a reduction in vaginal itching and burning (13). The existing evidence suggests that the absorption of oral curcumin is limited due to its brief stay in the stomach. However, a recent introduction to the Iranian pharmacy market is nanocurcumin products, which claim to withstand the acidic environment of the stomach for over 6 months. This extended durability potentially results in increased curcumin absorption in the intestine (14). However, there is limited evidence regarding the efficacy of this non-curcumin-based product, and more clinical trials are needed in this area. The current randomized clinical trial aimed to investigate the potential effect of oral nanocurcumin on HPV infection clearance in women with high-risk HPV genotypes.

Materials and Methods

Study Design

We performed a double-blind randomized clinical trial with placebo on 90 high-risk women who were referred to Pap smear screening in Iran in 2022.

Inclusion and Exclusion Criteria

The current study included women with high-risk Pap smear results and high-risk HPV typing aged 30-65 years. We excluded cases with candida cervicitis or vaginitis, trichomonas, and other infections; patients with known immunodeficiency or autoimmune disease; HIV-positive cases; long-term use of corticosteroids or immunosuppressants; and tobacco smoking. Pregnancy and having CIN2 or CIN3 in a cervical biopsy were the other exclusion criteria.

Randomization and Concealment

Study participants were randomly assigned to oral nanocurcumin intervention or placebo groups. We used computer-generated random numbers for randomization. The random numbers were between 0 and 1, and those lower than 0.5 were classified as 0, representing the placebo, and those above it were categorized as 1, representing the nanocurcumin intervention. Then, the assigned codes were written on paper and placed in a sealed envelope. We used 8-digit codes to number the pockets, and after enrolling each participant, we announced a specific code to the research team and asked them to assign the study participants into the compared groups (placebo vs. intervention) accordingly. Both research group and study participants were unaware of the codes and type of intervention as the groups were labeled using A and B.

Sample Size

Based on previous studies, the self-limiting proportion of HPV infection was considered to be 20% (13). Additionally, we took into account the marginal effect of nanocurcumin on HPV infection, estimated to be 30% (13). With a significance level (α) of 0.05 and a desired power of 80% for the study, the initial sample size was determined to be 40 participants in each group, totaling 80 participants overall. To account for potential loss to follow-up, we decided to enroll 90 participants in the study. The sample size calculation was conducted using Stata software (version 17.0). Case recruitment was based on convenient sampling, where participants were selected based on their ease of accessibility and availability. The study was performed on those individuals who expressed interest in participating voluntarily. During the case

enrollment, we had to exclude eight patients due to factors such as corticosteroid consumption, infection, and cervical intraepithelial neoplasia (CIN).

Intervention and Data Collection

The study was conducted on women aged 30-65 who underwent Pap smear screening and were considered high-risk according to HPV typing results. After randomization and assignment, the participants in the intervention group received 80 mg (in capsule form) of oral nanocurcumin on a daily basis. The duration of treatment was 4 months, and unless there was a menstruation period, the study participants in the intervention group received the same dose of treatment each day. The control group received a placebo with some dietary recommendations. We used a check list to collect baseline characteristics of the study participants, including age, marital status, history of pregnancy, any co-existing disorders, smoking status, drug use, alcohol use, and type of HPV.

Outcome Assessment

The primary outcome in the current study was HPV clearance according to post-treatment HPV qualitative and genotyping tests (Sacace Biotechnologies, Como, Italy). The diagnostic quality of the cervical smear (Pap smear) and adverse effects induced by treatment were the secondary outcomes that were investigated in this study. The outcome of each participant was recorded at the end of the follow-up.

Statistical Analysis

First, we checked the normality assumption using the Kolmogorov-Smirnov normality test. We described continuous variables using the mean and standard deviation if the normality assumption was met. Otherwise, we provided the median and interquartile range (IQR). As for dichotomous variables, we used frequency number and proportion. We compared baseline characteristics between the nanocurcumin and placebo groups using an independent t-test to ensure randomization had provided similar and comparable groups. Moreover, we used a chi-square test for the categorical variables. Finally, we compared post-treatment HPV clearance between the compared groups using the chi-square test. Moreover, the quality of the cervical smear was compared using an exact Fisher test. All the statistical analyses were performed using Stata software (Version 17.0, College Station, Texas, USA). A significance level of $P < 0.05$ was used to determine statistical significance.

Results

The study was conducted on 90 participants overall; however, two participants in the intervention group refused to continue the study protocol after randomization and assignment (Figure 1). Table 1 presents a comparison of baseline characteristics between the nanocurcumin intervention group and the control group. The average age of the study participants in the intervention group was 32.9 ± 7.5, while it was 33.1 ± 8.0 in the control

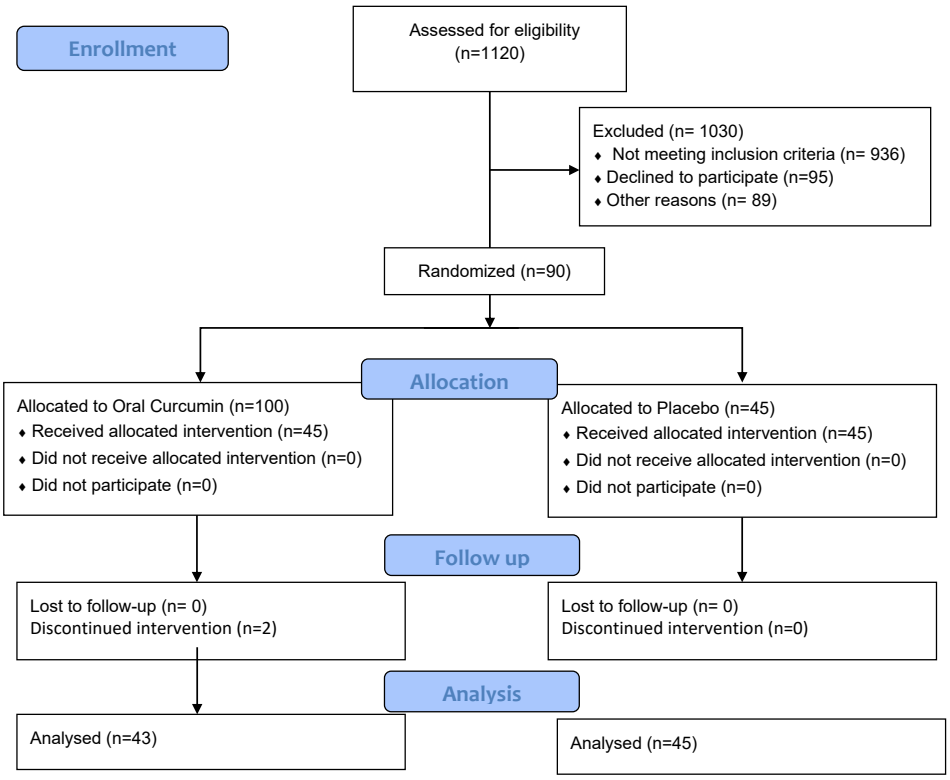

Figure 1. Flow Diagram of the Study.

group. There was no statistically significant difference in age between the two groups (P = 0.828). In terms of marital status, 30.2% of the patients in the intervention group were divorced/widow, compared to 42.2% in the control group. The prevalence of a history of pregnancy was 51.1% in the intervention group and 40.0% in the control group. The most prevalent comorbidity observed in both groups was hypothyroidism, with a prevalence of 11.5%. The prevalence of a history of drug use was 18.6% in the intervention group and 11.1% in the control group. No statistically significant difference was found between the two groups regarding these baseline characteristics (P > 0.05). Additionally, there was no statistically significant difference between the intervention and control groups in terms of history of alcohol use and smoking status (P > 0.05). The prevalence of the HPV-16 subtype was 16.2% in the nanocurcumin intervention group and 13.3% in the control group. Furthermore, the prevalence of the HPV-18 subtype was 20.9% in the intervention group and 17.7% in the placebo group. The observed differences in subtype prevalence were not statistically significant (P > 0.05) (Table 1).

Table 2 also indicates the clearance rates stratified by subtype for the intervention and control groups. In the intervention group, the HPV-16 clearance rate was 71.4%, whereas it was 50.0% in the control group. As for the HPV-18, the clearance rate in the intervention group was 77.8%, compared to 37.5% in the control group. No statistically significant difference was observed (P > 0.05). The clearance rate for all subtypes combined was 88.4% in the intervention group and only 68.9% in the control group. The observed differences in the clearance rates were statistically significant (P = 0.026) (Table 2).

Figure 2 illustrates the results of pre- and post-treatment Pap smear tests in the compared groups. The proportion of normal Pap smears in the pre-examination was 65.1% for the intervention group and 68.9% for the control group, and there was no statistically significant difference between the groups (P > 0.05). However, in the post-treatment Pap smear test, the percentage of normal

Table 1. Study Participants Baseline Characteristics in Intervention and Control Groups

Characteristics	Intervention (n=43)	Control group (n=45)	*P* Value[a]
Age, mean (SD)	32.9 (7.6)	33.1 (8.0)	0.828
Marital status, n (%)			
Single	13 (30.2%)	19 (42.2%)	
Married	30 (69.7%)	26 (57.8%)	0.384
Pregnancy, n (%)			
No	21 (48.8%)	27 (60.0%)	
Yes	22 (51.1%)	18 (40.0%)	0.290
Medical history, n (%)			
No comorbidity	36 (83.7%)	34 (75.6%)	
Hypertension	2 (4.6%)	6 (13.3%)	
Hyperthyroid	5 (11.6%)	5 (11.1%)	0.569
Drug history, n (%)			
No	35 (81.4%)	40 (88.9%)	
Yes	8 (18.6%)	5 (11.1%)	0.368
Alcohol use, n (%)			
No	40 (93.0%)	39 (86.7%)	
Yes	3 (7.0%)	6 (13.3%)	0.292
Smoking status, n (%)			
No	38 (86.0%)	33 (73.3%)	
Yes	5 (11.6%)	9 (20.0%)	0.197
No. of subtypes			
Only 1	33 (76.4%)	33 (73.3%)	
Two	7 (16.3%)	9 (20.0%)	
Three	2 (4.6%)	3 (6.7%)	
Four	1 (2.3%)	0 (0.0%)	0.723
HPV 16			
Negative	36 (83.7%)	39 (86.7%)	
Positive	7 (16.3%)	6 (13.3%)	0.561
HPV 18			
Negative	34 (79.1%)	37 (82.2%)	
Positive	9 (20.9%)	8 (17.8%)	1.00
HPV 16 & 18 combined			
Negative	27 (62.8%)	31 (68.9%)	
Positive	16 (37.2%)	14 (31.1%)	0.655

[a] Chi-square test.

Table 2. Clearance Rate of HPV, HPV 16, HPV18, and HPV 16 and 18 in Nanocurcumin Intervention and Placebo Groups

Characteristics	Intervention	Control Group	*P* Value[a]
HPV 16	5/7 (71.4%)	3/6 (50.0%)	0.124
HPV 18	7/9 (77.8%)	3/8 (37.5%)	0.131
HPV 16&18	12/16 (75.0%)	6/14 (42.8%)	0.029
Overall	38/43 (88.4%)	31/45 (68.9%)	0.001

[a] Independent samples *t* test.

results increased to 75.6% in the intervention group, while it decreased to 60.0% in the control group, which was significantly lower than the intervention group ($P < 0.05$). The most common type of abnormality reported in the post-treatment Pap smear in the control group was ACS-US, which was observed in 15.5% of cases. No ACS-US cases were observed in the intervention group (Figure 2).

Discussion

The present study was a double-blind randomized clinical trial conducted to evaluate the impact of oral nanocurcumin on HPV infection clearance in high-risk women who underwent Pap smear screening tests. The intervention group received a daily dose of 80 mg of oral nanocurcumin for a duration of 4 months as part of their treatment, while the control group received a placebo. The results of the study demonstrated that oral nanocurcumin enhanced HPV clearance, both in high-risk subtypes such as subtype 16 and subtype 18, as well as in other low-risk subtypes. Additionally, the use of oral nanocurcumin resulted in more favorable outcomes in post-treatment Pap smears compared to the placebo group. The proportion of abnormal Pap smears after treatment in the nanocurcumin group was 24.5%, which was significantly lower than the 30% abnormal results observed in the placebo group.

It is well known that HPV infections can resolve on their own without treatment, as the immune system is often able to clear the virus. The clearance rate of HPV infections varies and can be influenced by various factors. In the current study, the clearance rate of high-risk HPV in the placebo group was approximately 43%, which was lower than what has been reported in previous studies. For instance, a population-based study conducted in Colombia reported a clearance rate of 77.0% for women with positive HPV infections during the first 6 months of their follow-up (15). The self-clearance rate in a study conducted among Cameroonian women was reported at 79.5% over a 12-month follow-up period (16). Similar findings were also reported by Basu et al (13). These studies had longer follow-up periods, ranging from 6 months to 1 year. In comparison, the current study had a follow-up period of 4 months, which might explain the slight difference in clearance rates observed between our study and previous findings. A longer follow-up period allows for a greater likelihood of observing spontaneous clearance of HPV infections.

Nonetheless, the results of our study were consistent with previous research, as we reported a higher HPV clearance rate in the nanocurcumin intervention group compared to the placebo group. Basu et al (13), supporting our results, also reported a higher HPV clearance rate in the curcumin vaginal cream group compared to the placebo group. However, the observed difference in their study was not statistically significant, which could be attributed to a small sample size (13). Indeed, in addition to clinical studies, there have been in vitro and experimental studies suggesting that nanocurcumin can enhance the clearance rate of HPV infections and exhibit

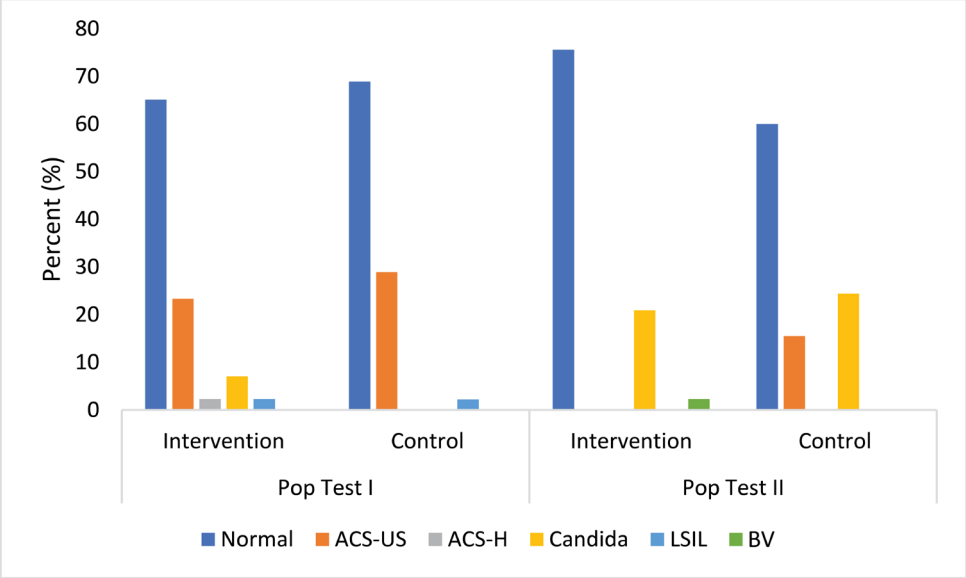

Figure 2. Comparison of Pop Smear Test Results Between Intervention and Control Group Before and After Study. (ASC-US): Atypical squamous cells of undetermined significance; (ASC-H): High grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; BV: Bacterial vaginosis.

antiviral effects (17). One study conducted by Einbond et al investigated the efficacy of a botanical mixture called TriCurin, which contains curcumin, against HPV-positive cells. They found that TriCurin exhibited effectiveness against W12 cells derived from pre-cancerous cervical lesions (18). The study highlighted the inhibitory role of TriCurin in the p53 pathway, which is involved in cell cycle regulation and tumor suppression. Another experimental study focused on a nanocurcumin-based cream and its effects on HPV-positive cervical cells (18). The researchers demonstrated that the nanocurcumin-based cream was capable of destroying HPV-positive cells. They proposed that nanocurcumin could suppress the E6 transforming antigen, a viral protein produced by high-risk HPV types, and simultaneously inhibit the expression of the procarcinogenic protein epidermal growth factor receptor while inducing p53, a tumor suppressor protein (18). The effect of nanocurcumin on various cellular processes, including NF-κB transportation to the cell nucleus, reduction in the expression of oncogene genes of HPV, and induction of apoptosis in HPV-infected cells, has the potential to enhance HPV clearance and prevent the development of cervical cancer (19). A case report study, which involved the application of nanocurcumin to a menopausal woman suffering from HPV infection and vaginal warts, yielded promising outcomes. The study demonstrated that nanocurcumin could be utilized as an effective therapeutic approach to clear HPV infection and treat genital warts (20).

The current study represented one of the initial attempts to investigate the impact of oral nanocurcumin on HPV clearance in high-risk women. To enhance the validity of our findings, we employed a robust study design that incorporated randomization. Additionally, to minimize potential biases, the study was conducted in a double-blind manner, ensuring that both clinicians and study participants were unaware of the intervention. However, it is important to acknowledge certain limitations that should be taken into consideration when interpreting our findings. The small sample size, particularly for subgroup analysis, was a primary limitation of the study. This may have limited our ability to detect statistically significant differences and generalize the results to a wider population. Additionally, the lack of a human-based trial restricted the generalizability of our findings, as animal or in vitro studies may not fully represent the complexities of human physiology. Furthermore, the exclusion of certain participants due to non-compliance with the assigned treatment and a lack of willingness to participate due to the blinding process could have introduced selection bias and affected the overall representativeness of the study sample. Additionally, the relatively short duration of follow-up compared to previous studies was another limitation. This shorter follow-up period may have contributed to the lower clearance rate observed in the placebo group, as longer observation periods are generally associated with higher rates of spontaneous clearance.

Conclusion

In conclusion, based on the current study and available evidence, it can be concluded that oral nanocurcumin has the potential to increase the clearance rate of HPV infections. Additionally, the treatment with oral nanocurcumin appears to be safe, with minimal major adverse events reported. However, it is important to note that the current study has certain limitations, including a small sample size and a relatively short follow-up period. Therefore, further studies with larger sample sizes and longer follow-up periods are needed to validate these findings and provide more robust evidence regarding the efficacy and safety of oral nanocurcumin in the treatment of HPV infections.

Authors' Contribution

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Project administration: Maryam Mohsenikia.
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Supervision: Somayeh Nikfari.
Validation: Amir Almasi-Hashiani.
Visualization: Somayeh Nikfari, Maryam Mohsenikia.
Writing–original draft: Maryam Mohsenikia.
Writing–review & editing: Maryam Mohsenikia.

Conflict of Interests

The authors declare that they have no conflict of interest.

Ethical Issues

The study received ethical approval from the Arak University of Medical Sciences Ethics and Review Board, with the assigned ethics code IR.ARAKMU.REC.1401.076. Prior to their participation, all the patients were fully informed about the study protocol, and informed consent was obtained from each participant. The trial was registered at the Iran Clinical Trial Registry with the registry code IRCT20220629055314N1.

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