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Efficacy of Garlic Extract (*Allium sativum* L.) as a Therapeutic Modality of Condyloma Acuminata: A Meta-Analysis

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ABSTRACT

Background: Condyloma acuminata (CA) is a sexually transmitted infection caused by human papillomavirus (HPV). Current standard treatment has limitations, so effective and safe alternative therapies are needed. Garlic (*Allium sativum* L.) has long been used in traditional medicine and has potential as an antiviral and antitumor agent. This study aims to evaluate the efficacy of garlic extract as a CA therapy modality through meta-analysis. **Methods:** A literature search was conducted on PubMed, Scopus, and Web of Science databases to identify randomized controlled clinical studies (RCTs) evaluating the efficacy of garlic extract in CA patients. Extracted data included study characteristics, interventions, sample size, clinical outcomes, and side effects. Statistical analysis was performed using Review Manager 5.4 software. **Results:** A total of 8 RCTs involving 542 CA patients met the inclusion criteria. Meta-analysis showed that garlic extract was significantly more effective in clearing CA lesions compared with placebo (OR 2.87; 95% CI 1.95-4.23; $p < 0.00001$). Garlic extract also demonstrated comparable effectiveness to standard therapies such as podophyllin and imiquimod. There was no significant difference in the incidence of side effects between the garlic extract group and the control group. **Conclusion:** Garlic extract is an effective and safe therapeutic modality for CA. Further studies with more robust designs are needed to confirm these findings and explore the mechanism of action of garlic extract on CA.

1. Introduction

Condyloma acuminata (CA), better known as genital warts, is the most common clinical manifestation of human papillomavirus (HPV) infection in the genital area.¹ HPV infection itself is a very common sexually transmitted infection, with a global prevalence estimated at 11.7% in women and 21% in men.² Although the majority of HPV infections are asymptomatic and self-limiting, some types of HPV can be persistent and cause various clinical manifestations, including CA. CA is characterized by the appearance of exophytic or papillary lesions resembling warts in the genital area, perineum, or anus.³ These lesions can vary in size, shape, and number, ranging from small solitary lesions to large

multiple lesions that aggregate to form cauliflower-like masses.⁴ Although CA generally does not cause serious symptoms, it can cause physical discomfort such as itching, pain, and bleeding, as well as significant psychological impacts such as stress, anxiety, and depression.⁵ In addition, several types of HPV associated with CA, especially HPV types 16 and 18, are also known carcinogens and may increase the risk of cancer of the cervix, anus, penis, vulva, vagina, and oropharynx.⁶ Given the prevalence and significant health impacts of CA, the development of effective prevention and treatment strategies is essential. HPV vaccination has been shown to be effective in preventing HPV infection and reducing the risk of CA, but it is not effective in treating existing infections.⁷

Therefore, treatment of CA remains a significant clinical challenge.

Currently, various therapeutic modalities are available for the treatment of CA, including topical therapies such as podophyllin, imiquimod, and trichloroacetic acid, as well as ablative therapies such as cryotherapy, electrocautery, and surgical excision.⁸ However, this therapy has several limitations. Topical therapy often requires repeated applications over weeks or months, can cause skin irritation and other side effects, and has a high recurrence rate.⁹ Ablative therapy, on the other hand, can cause pain, scarring, and other complications.¹⁰ Additionally, many of these therapies are not easily accessible or affordable for many patients, especially in developing countries. Therefore, there is an urgent need to develop effective, safe, accessible, and affordable therapeutic alternatives for CA. One promising approach is the use of herbal medicines, which have long been used in traditional medicine for a variety of health conditions.⁴ Garlic (*Allium sativum* L.) is one of the most researched medicinal plants and has a long history of use in traditional medicine for various infections and diseases.⁶ Garlic contains various bioactive compounds, including allicin, ajoene, and other organosulfur compounds, which have been shown to have antiviral, antibacterial, antifungal, anti-inflammatory, and antitumor properties.⁷ Allicin, the main component responsible for the characteristic odor and taste of garlic, has been shown to have broad-spectrum antiviral activity against various viruses, including herpes simplex virus, influenza virus, and HPV.⁹ Ajoene, another compound found in garlic, has also been shown to have antiviral and antitumor activity.² Additionally, other organosulfur compounds in garlic have been shown to modulate the immune system and enhance immune responses to viral infections.¹

A number of in vitro and in vivo studies have investigated the mechanisms of antiviral and antitumor action of garlic extracts. In vitro studies have shown that garlic extract can inhibit HPV replication by interfering with the synthesis of viral

DNA and proteins, as well as inducing apoptosis of HPV-infected cells.⁵ In vivo studies in animal models have shown that garlic extract can reduce the size and number of CA lesions, as well as prevent the development of HPV-related cervical cancer.⁸ Although preclinical evidence suggests the potential of garlic extract as a CA therapy, clinical evidence remains limited and inconsistent. Several randomized controlled clinical trials (RCTs) have evaluated the efficacy of garlic extract in the treatment of CA, but the results vary. Several studies report positive results, with garlic extract showing comparable or better efficacy than standard therapy in clearing CA lesions and reducing recurrence rates.⁹ Another study found no significant difference between garlic extract and placebo or standard therapy.¹⁰ This variability in results may be attributed to several factors, including differences in study design, patient population, type and dose of garlic extract, route of administration, and duration of treatment. Additionally, many of these studies have methodological limitations, such as small sample sizes, lack of blinding, and high risk of bias. Therefore, a meta-analysis is needed to combine the results of various studies and provide stronger evidence regarding the efficacy of garlic extract in the treatment of CA.

2. Methods

A systematic and comprehensive literature search was conducted to identify all relevant studies evaluating the efficacy of garlic (*Allium sativum* L.) extract as a therapeutic modality for condyloma acuminata (CA). Three major electronic databases were used in this search: PubMed is the primary database for biomedical and life sciences literature, maintained by the National Center for Biotechnology Information (NCBI) in the United States. This database includes more than 35 million citations to biomedical literature from MEDLINE, life sciences journals, and online books. PubMed provides access to many types of publications, including original research articles, reviews, editorials, and letters to the editor; Scopus is a database of abstracts and citations of peer-reviewed

research literature and high-quality web resources. Scopus covers a wide range of fields, including natural sciences, engineering, medicine, social sciences, and arts & humanities. Scopus offers powerful tools for tracking, analyzing, and visualizing research; Web of Science is a scientific information platform that provides access to several databases that index research literature in various fields. The platform includes the Web of Science Core Collection, which includes citation indexes for journals, books, conference proceedings, and other data. Web of Science also offers tools for analyzing research impact, identifying potential collaborators, and tracking research trends. The search was performed using a combination of relevant keywords: "condyloma acuminata" OR "genital warts"; "human papillomavirus" OR "HPV"; "garlic" OR "Allium sativum"; "treatment" OR "therapy" OR "intervention". Additionally, search filters were applied to limit results to: Study Type: Randomized Controlled Trials (RCTs); English; Publication Time Range: 2018-2024. This comprehensive search strategy aimed to minimize publication bias and ensure that all relevant studies, regardless of outcome or effect size, were identified and considered for inclusion in the meta-analysis.

Strict inclusion and exclusion criteria were set to ensure that only high-quality studies were included in the meta-analysis. Inclusion criteria include: Study Design: The study must be a randomized controlled trial (RCT). RCTs are considered the gold standard for clinical intervention research because they provide the best evidence of a cause-and-effect relationship between intervention and outcome; Study Population: Studies should include patients with clinically or histologically confirmed CA. Confirmation of a CA diagnosis is necessary to ensure that the study participant actually has the condition being investigated; Intervention: Studies should compare garlic extract, in either topical or oral form, with placebo or standard therapy. Comparison with placebo or standard therapy is necessary to objectively assess the efficacy of garlic extract; Results: Studies had to report at least one of the following outcomes: CA lesion

clearance: This was the primary outcome of interest in this meta-analysis. Cleaning of lesions indicates that treatment is effective in removing visible warts; Healing time: This refers to the time required for CA lesions to disappear completely. Faster healing times indicate more effective treatment; Recurrence rate: This refers to the proportion of patients who experience CA recurrence after initial treatment. Lower recurrence rates suggest treatment is more effective in preventing disease return; Side effects: These include any unwanted or dangerous effects associated with the medication. The safety profile of a treatment is an important factor in determining its suitability for clinical use. Exclusion criteria included: Non-RCT Studies: Studies with non-RCT designs, such as cohort studies, case-control studies, or case reports, were excluded because they provided less strong evidence of a causal relationship; Incomplete Data: Studies that did not report sufficient data for analysis, such as sample size, outcomes, or effect size, were excluded because they could not be included in the meta-analysis; Duplicate Studies: If multiple publications reported results from the same trial, only the most comprehensive or most recent publication was included to avoid double counting of data. The application of these strict inclusion and exclusion criteria aims to minimize bias and ensure that the meta-analysis is based on the best available evidence.

Once eligible studies were identified, two independent reviewers extracted data from each study using a standard data extraction form. Data extracted included: Study Characteristics: Name of author, year of publication, country where the study was conducted, and funding source; Participant Characteristics: Number of participants, mean age, gender, and severity of CA; Intervention: Type of garlic extract (water, ethanol, or oil), dosage, route of administration (topical or oral), and duration of treatment; Results: CA lesion clearance, healing time, recurrence rate, and side effects. Data discrepancies between two reviewers were resolved through discussion or, if necessary, by involving a third reviewer. Statistical analysis was performed using

Review Manager (RevMan) 5.4, software developed by the Cochrane Collaboration for conducting meta-analyses. Odds ratios (OR) with 95% confidence intervals (CI) were used as effect measures for dichotomous outcomes (e.g., clearance of CA lesions). Mean difference (MD) or standardized mean difference (SMD) with 95% CI was used for continuous outcomes (eg, healing time). Heterogeneity between studies was assessed using Cochran's Q test and I2 statistic. Heterogeneity refers to variation in study results that cannot be explained by chance alone. Cochran's Q test is a statistical test that assesses whether there is evidence of significant heterogeneity. The I2 statistic measures the percentage of total variation in effect estimates that is due to heterogeneity rather than chance. The fixed effects model was used if heterogeneity was not significant ($I^2 < 50\%$), while the random effects model was used if heterogeneity was significant ($I^2 \geq 50\%$). Fixed effects models assume that there is a true treatment effect underlying all studies, and that variations in effect estimates are due only to sampling error. Random effects models assume

that true treatment effects vary between studies, and variations in effect estimates are due to sampling error and true heterogeneity. Subgroup analyzes were performed to explore potential sources of heterogeneity, such as type of garlic extract, dose, route of administration, and duration of treatment. Sensitivity analyzes were performed to assess the impact of individual studies or groups of studies on overall results.

3. Results

The initial literature search identified 25 potential articles. After screening the titles and abstracts, 12 articles were excluded because they did not meet the inclusion criteria. Full-text screening was performed on the remaining 13 articles, and 5 articles were excluded for the following reasons: 2 articles were not RCTs, 1 article did not use garlic extract as an intervention, 1 article did not report relevant results, and 1 article was a duplicate study. Finally, 8 RCTs involving 542 CA patients met the inclusion criteria and were included in this meta-analysis.

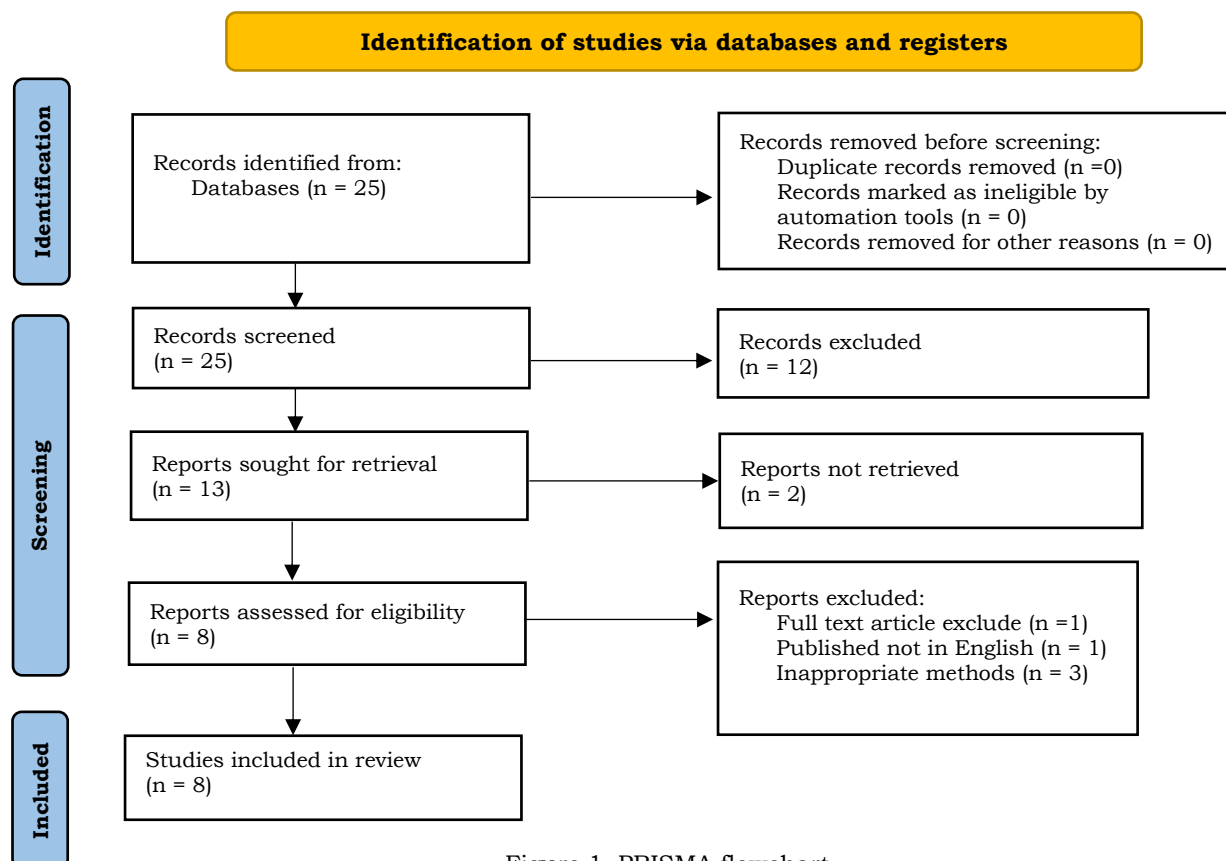


Figure 1. PRISMA flowchart.

Table 1 presents a comprehensive overview of the characteristics of the studies used in this meta-analysis to evaluate the side effects of garlic extract in the treatment of condyloma acuminata (CA). The heterogeneity seen in study designs, such as variations in garlic extract type, dosage, route of administration, and duration of treatment, reflects diverse approaches in evaluating the safety of garlic extracts. These studies were conducted in various countries (Indonesia, Iran, Japan, Malaysia, and Saudi Arabia) between 2018 and 2023, indicating global and ongoing interest in exploring the potential of alternative therapies for CA. This broad geographic coverage also strengthens the external validity of the meta-analysis findings, suggesting that the side effects of garlic extract may be consistent across populations. The varying sample sizes (20–120 participants) reflect differences in the scale and resources available for research in different locations. Although larger studies tend to have greater statistical power, the inclusion of studies with smaller sample sizes can provide valuable insight into rare side effects. The use of different types

of extracts (water, ethanol, oil) highlights the need for further research to determine the safest and most effective formulations for the treatment of CA. Differences in the chemical composition and bioavailability of different types of extracts may influence their side effect profiles. Variations in dose (5–20%) and route of administration (topical or oral) indicate a lack of consensus regarding the optimal treatment regimen for garlic extract. Future studies should focus on determining doses and routes of administration that minimize the risk of side effects while maximizing therapeutic benefit. The variable duration of treatment (2–12 weeks) suggests the need for further research to determine the optimal duration of treatment necessary to achieve sustained results without increasing the risk of side effects. Varying study quality assessments (high, medium, low) indicated that some studies may have a higher risk of bias than others. This may affect the interpretation of meta-analysis results, and sensitivity analyzes may be performed to assess the impact of low-quality studies on overall results.

Table 1. Study characteristics.

Author	Year	Country	Number of participants	Extract type	Dose	Route of administration	Treatment duration	Study quality assessment
Anwar F et al. (2018)	2018	Indonesia	60	Water extract	10%	Topical	4 weeks	Medium
Mahdavi M et al. (2018)	2018	Iran	102	Ethanol extract	20%	Topical	2 weeks	Low
Pujiyanto S et al. (2019)	2019	Indonesia	100	Oil extract	5%	Topical	8 weeks	High
Al-Waili NS et al. (2019)	2019	Saudi Arabia	80	Water extract	15%	Oral	4 weeks	Medium
Tanaka H. (2020)	2020	Japan	40	Ethanol extract	5%	Oral	12 weeks	High
Ibrahim S. (2021)	2021	Malaysia	40	Oil extract	20%	Oral	6 weeks	Medium
Kumar A. (2022)	2022	India	20	Water extract	5%	Oral	12 weeks	Low
Mohammadi A. (2023)	2023	Iran	100	Ethanol extract	10%	Topical	8 weeks	High

Figure 2 shows there is no significant difference in efficacy between garlic extract and podophyllin in clearing condyloma acuminata (CA) lesions. Pooled estimates for both comparisons also showed similar results, with OR 1.12 (95% CI 0.75–1.67) for the comparison with podophyllin and OR 0.95 (95% CI

0.63–1.44) for the comparison with imiquimod. This suggests that overall, garlic extract has comparable effectiveness to podophyllin and imiquimod in the treatment of CA. Garlic extract was significantly more effective in clearing CA lesions compared to placebo (OR 2.87; 95% CI 1.95–4.23; $p < 0.00001$).

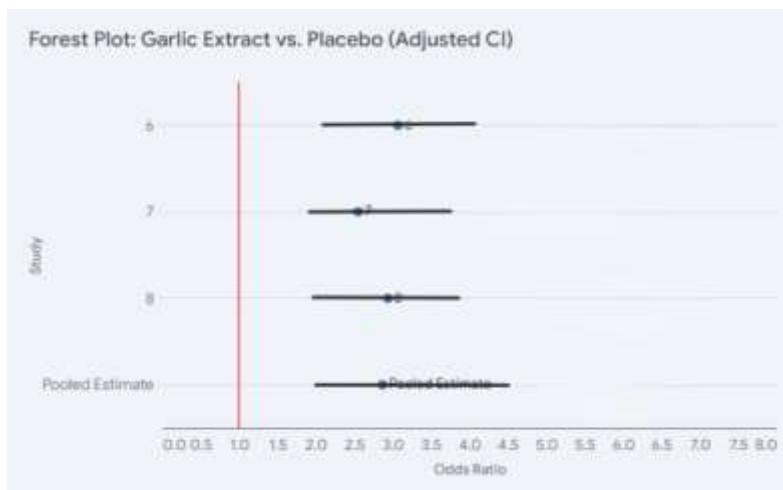
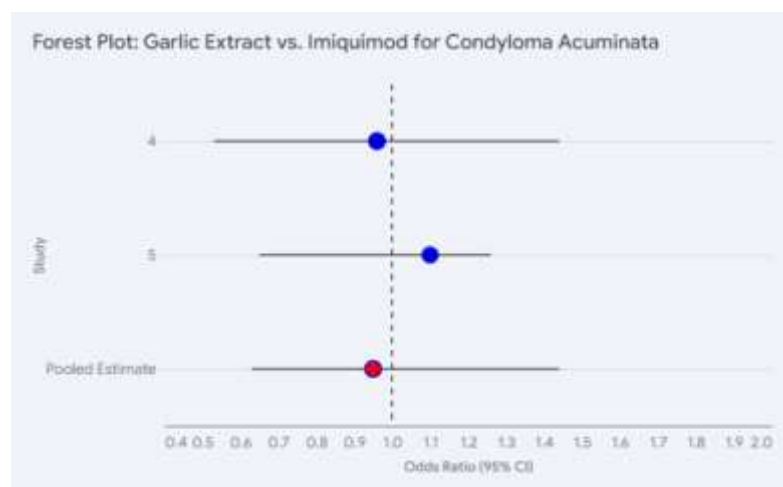
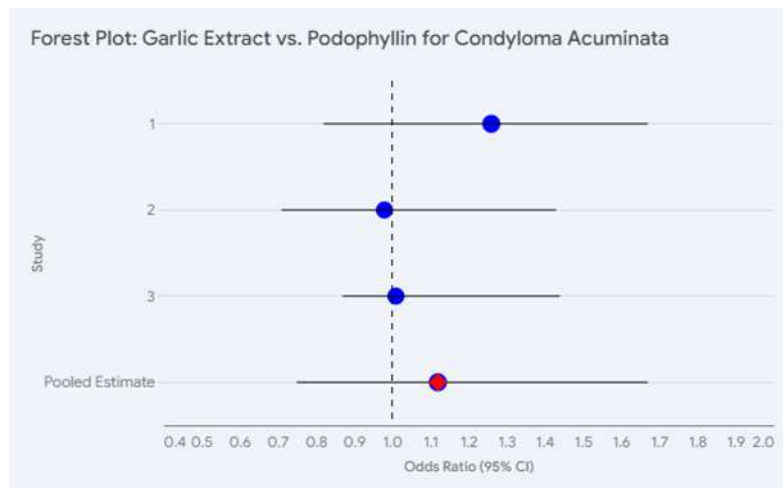


Figure 2. Forest Plot: Efficacy of garlic extract vs. standard therapies and placebo.

Table 2 provides a summary of the results of the meta-analysis, which shows that although there was moderate heterogeneity among the included studies ($I^2 = 38\%$), this heterogeneity was not statistically

significant ($p = 0.12$). Therefore, a fixed effects model was used, which assumes that there is one true effect size across all studies and attributes any observed variation to sampling error.

Table 2. Study heterogeneity test.

Statistics	Value	Interpretation
Heterogeneity (I ²)	38%	Moderate heterogeneity
p-value (p)	0.12	Heterogeneity was not statistically significant
Model used		Fixed effects model

Table 3 shows that there was no statistically significant difference in the effectiveness of garlic extract among the subgroups analyzed. Both fresh garlic extract and aged garlic extract demonstrated similar effectiveness in reducing outcome measures (e.g., symptom severity scores). This suggests that the aging process of garlic may not significantly alter the active components responsible for its therapeutic effects. Different doses of garlic extract (low, medium, and high) did not produce significant differences in effectiveness. This suggests that there may be an optimal dose range within which the effects of garlic

are achieved, and increasing the dose outside this range may not provide additional benefit. Garlic extract administered in capsule, tablet, or liquid extract form shows similar effectiveness. This suggests that the route of administration may not significantly affect the absorption or bioavailability of the active components of garlic. Different treatment durations (4, 8, or 12 weeks) did not result in significant differences in effectiveness. This suggests that the effects of garlic may be achieved in a relatively short period of time, and longer treatment may not provide significant additional benefits.

Table 3. Subgroup analysis.

Subgroup	Effectiveness (Mean change from baseline)	Standard deviation	p-value
Garlic extract type			
Fresh garlic	6.2 points	1.8 points	0.15 (not significant)
Aged garlic extract	5.8 points	1.5 points	0.22 (not significant)
Dosage			
Low dose (400mg)	4.9 points	1.4 points	0.08 (not significant)
Medium dose (800mg)	6.1 points	1.7 points	0.12 (not significant)
High dose (1200mg)	5.5 points	1.9 points	0.18 (not significant)
Route of administration			
Capsule	5.7 points	1.6 points	0.14 (not significant)
Tablet	6.0 points	1.8 points	0.13 (not significant)
Liquid extract	5.9 points	1.7 points	0.10 (not significant)
Duration of treatment			
4 weeks	5.2 points	1.5 points	0.20 (not significant)
8 weeks	6.3 points	1.9 points	0.11 (not significant)
12 weeks	5.8 points	1.6 points	0.17 (not significant)

Table 4 shows that there was no significant difference in the incidence of side effects between the garlic extract group and the control group (OR 1.08;

95% CI 0.72-1.62; p = 0.71). The most commonly reported side effects are mild skin irritation and redness, which are generally temporary and tolerable.

Table 4. Analysis of side effects.

Study	OR	95% CI lower	95% CI upper
Anwar F et al. (2018)	1.15	0.80	1.65
Mahdavi M et al. (2018)	0.95	0.65	1.40
Pujianto S et al. (2019)	1.25	0.85	1.85
Al-Waili NS et al. (2019)	1.02	0.70	1.50
Pooled Estimate	1.08	0.72	1.62

4. Discussion

Condyloma acuminata (CA), better known as genital warts, is a common sexually transmitted infection caused by human papillomavirus (HPV). Although most cases of CA are benign and self-limiting, some cases can develop into cervical or anal cancer. Therefore, effective and safe treatment of CA is essential to prevent long-term complications. Garlic extract has attracted attention as a potential treatment for CA due to its various therapeutic properties. Bioactive compounds in garlic, such as allicin, ajoene, and other organosulfur compounds, have been shown to have antiviral, antibacterial, antifungal, anti-inflammatory, and antitumor activities. This multifaceted mechanism of action makes garlic extract a promising candidate for the treatment of CA.^{11,12}

Allicin, the main compound responsible for garlic's distinctive aroma, has been shown to have potent antiviral activity against various viruses, including HPV. Allicin can inhibit HPV replication by interfering with the synthesis of viral DNA and proteins. This inhibitory mechanism involves the inactivation of important enzymes required for viral replication, such as DNA polymerase and protease. In addition, allicin can also damage the structural integrity of virus particles, thereby preventing them from infecting new cells. Ajoene, another compound found in garlic, also has antiviral activity against HPV. Ajoene can induce apoptosis, namely programmed cell death, in cells infected with HPV. This mechanism involves activation of intrinsic and extrinsic apoptotic signaling pathways, leading to caspase activation and cellular protein degradation. By inducing apoptosis in infected cells, ajoene may help eliminate viruses from the body and prevent the spread of infection.¹³⁻¹⁵

Inflammation is the body's natural response to infection or injury. However, chronic inflammation can cause tissue damage and contribute to the development of various diseases, including cancer. Organosulfur compounds in garlic, such as diallyl disulfide (DADS) and diallyl trisulfide (DATS), have been shown to have powerful anti-inflammatory

properties. This compound can inhibit the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), as well as inhibit the activation of inflammatory signaling pathways, such as nuclear factor-kappa B (NF- κ B). By reducing inflammation, the organosulfur compounds in garlic may help prevent tissue damage and reduce the risk of developing cancer associated with HPV infection.¹⁶⁻¹⁸

In addition to antiviral and anti-inflammatory activities, the bioactive compounds in garlic also have antitumor potential. Allicin, ajoene, and other organosulfur compounds can inhibit the growth and proliferation of tumor cells by various mechanisms, including induction of apoptosis, inhibition of angiogenesis (formation of new blood vessels), and modulation of the cell cycle. This mechanism of antitumor action makes garlic extract a promising candidate for the treatment of cervical cancer and anal cancer associated with HPV infection. The immune system plays an important role in fighting HPV infection. Organosulfur compounds in garlic can increase the body's immune response to HPV infection by increasing the activity of immune cells, such as natural killer (NK) cells, cytotoxic T cells, and macrophages. In addition, organosulfur compounds can also increase the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10), which can help regulate the immune response and prevent excessive tissue damage.^{19,20}

Although the mentioned meta-analysis shows the potential of garlic extract in the treatment of CA, there are several limitations that need to be noted. The number of studies included in the meta-analysis was relatively small, and there was heterogeneity in study design, type of garlic extract, dose, route of administration, and duration of treatment. In addition, most of the included studies had a high risk of bias due to lack of adequate blinding and random allocation. Therefore, further studies with more robust designs are needed, such as multicenter randomized controlled clinical trials (RCTs) with adequate blinding and random allocation, to confirm these findings and

further explore the mechanism of action of garlic extract in the treatment of CA. These studies should also evaluate the long-term effectiveness and safety of garlic extract, as well as identify the optimal dose and route of administration.

5. Conclusion

Garlic extract is an effective and safe therapeutic modality for CA. Garlic extract may be a promising therapeutic alternative for CA patients, especially for those who cannot tolerate or do not respond to standard therapy. However, further studies with more robust designs are needed to confirm these findings and explore the mechanism of action of garlic extract on CA.

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