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Probiotics as a Therapeutic Strategy in Ovarian Cancer: Insights from Preclinical and Clinical Evidence

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A B S T R A C T

Objective: Ovarian cancer remains one of the most prevalent malignancies affecting women, and current treatment strategies often have significant limitations. In recent years, probiotics have emerged as a promising adjunctive therapy alongside standard treatments. By modulating the immune system, influencing gut microbiota, and reducing inflammation, probiotics have the potential to improve outcomes for patients with ovarian cancer. This review aims to provide a comprehensive examination of the therapeutic role of probiotics in ovarian cancer management.

Methods: A literature search was performed across PubMed, Scopus, Google Scholar, and ISI Web of Science to identify studies evaluating the effects of probiotics on ovarian cancer. Evidence from in vitro, animal, and clinical studies was collected and analyzed, with a focus on probiotic effects on tumor growth, progression, and therapeutic response.

Results: Current evidence suggests that probiotics may confer multifaceted benefits in ovarian cancer management. Strains such as *Lactobacillus rhamnosus* (including LGG), *Lactobacillus acidophilus*, and *Lactobacillus plantarum* have demonstrated the ability to inhibit tumor-associated signaling pathways, reduce cancer cell migration and invasion, and enhance immune responses. Additionally, *Bifidobacterium longum*, *Bifidobacterium breve*, and *Bifidobacterium animalis* have been associated with decreased drug resistance, modulation of inflammatory responses, and restoration of gut microbiota composition. Furthermore, bacteria such as *Akkermansia muciniphila* and *Limosilactobacillus reuteri* have shown promising effects by enhancing antitumor immunity and improving the efficacy of complementary therapies. Collectively, these findings indicate that probiotics may serve as valuable adjuncts to conventional ovarian cancer treatments, potentially improving therapeutic outcomes and mitigating adverse effects. Nonetheless, further large-scale clinical trials are warranted.

Conclusion: Based on preclinical and limited clinical evidence, probiotics may serve as a safe complementary approach in ovarian cancer therapy; however, their therapeutic efficacy remains inconclusive. Consequently, they should be regarded as an adjunctive strategy rather than a standalone treatment.

Keywords: Probiotics, Ovarian cancer, Therapy, Microbiome, Adjunctive treatment

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Introduction

Ovarian cancer is among the deadliest malignancies of the female reproductive system, primarily because its early symptoms are vague and often overlooked, resulting in frequent diagnoses at advanced stages [1]. This delay significantly contributes to the lower survival rates observed in ovarian cancer patients compared with other gynecologic cancers [2]. The disease imposes a high mortality burden, substantial treatment costs, and profound physical and psychological consequences, making it a major challenge for global healthcare systems [2].

The etiology of ovarian cancer is multifactorial, encompassing genetic, hormonal, environmental, and lifestyle components [3]. Inherited mutations particularly in genes involved in DNA repair family history of cancer, advanced age, nulliparity, and prolonged estrogen exposure are well-established risk factors [3]. Additionally, chronic inflammation and immune dysregulation have emerged as critical contributors to tumor initiation and progression, highlighting the importance of the microbiota in modulating immune responses [4].

From a pathophysiological perspective, ovarian cancer is characterized by uncontrolled proliferation of ovarian epithelial cells, disruption of cell cycle regulatory pathways, evasion of apoptosis, and a high propensity for invasion and metastasis [5]. The tumor microenvironment comprising immune cells, cytokines, and inflammatory mediators' plays a central role in tumor growth and therapy resistance [6]. Growing evidence suggests that microbial imbalances, or dysbiosis particularly along the gut–immune axis may facilitate ovarian cancer progression by amplifying systemic inflammation and suppressing anti-tumor immune responses [5,6].

Beyond its direct threat to survival, ovarian cancer is associated with a wide range of physical and psychological complications. Chronic pelvic pain, gastrointestinal disturbances, ascites, weight loss, fatigue, and diminished quality of life are common [7]. Late-stage diagnosis is often accompanied by extensive involvement of the peritoneum and adjacent organs, further complicating management and worsening prognosis [8].

Despite advances in diagnostic and therapeutic techniques, outcomes remain suboptimal, underscoring the urgent need for complementary and innovative strategies. Standard treatment approaches typically include cytoreductive surgery, chemotherapy, and, in select cases, radiotherapy or targeted therapies [9]. Although these interventions can improve survival, they are often associated with significant adverse effects, including nausea, vomiting, immunosuppression, neuropathy, gastrointestinal disturbances, infertility, and psychological distress [10]. Moreover, drug resistance and disease recurrence remain major therapeutic challenges, emphasizing the need for adjunctive strategies with lower toxicity [10].

Probiotics defined as live beneficial microorganisms play a critical role in maintaining microbial balance, enhancing immune function, and modulating inflammation [11]. Their application in the prevention and treatment of various conditions including gastrointestinal disorders, metabolic diseases, infections, and inflammatory diseases is well-documented [12]. Recently, growing attention has been given to the potential of probiotics to modulate immune responses, inhibit cancer cell proliferation, and mitigate the adverse effects of anti-cancer therapies. Several studies have reported promising effects in malignancies such as breast and ovarian cancers [13,14].

Given the pathophysiological similarities between hormone- and inflammation-associated cancers, including breast and ovarian cancers, investigating the role of probiotics in ovarian cancer management is particularly relevant. This review aims to synthesize and critically evaluate current preclinical and clinical evidence regarding the impact of probiotics in ovarian cancer. By consolidating existing knowledge, this work may inform the design of future studies and support the development of novel therapeutic strategies in this domain.

Methods

This study was conducted as a narrative review, aiming to synthesize and critically analyze existing evidence on the role of probiotics in the management and treatment of ovarian cancer. A systematic search was performed across reputable international databases, including PubMed, Scopus, Web of Science, and Google Scholar. To capture relevant studies published in Persian, the SID and Magiran databases were also searched.

The search targeted publications from 2010 to 2025 to ensure inclusion of the most current and reliable evidence regarding the effects of probiotics on ovarian cancer, their underlying molecular and immune mechanisms, and their potential to mitigate adverse effects associated with conventional treatments. A combination of keywords and standardized MeSH terms was employed, with “probiotics” and “ovarian cancer” serving as the primary search terms.

This review included original research articles, narrative and systematic reviews, and clinical trials that examined the effects of probiotics in women with ovarian cancer. Only studies published in English or Persian with accessible full texts and reporting outcomes related to clinical effects, immunological responses, anti-inflammatory properties, molecular mechanisms, or alterations in gut microbiota were considered.

Exclusion criteria comprised studies unrelated to ovarian cancer or probiotics, abstracts, conference reports, letters to the editor, and publications without full-text availability. Additionally, studies with low methodological quality, insufficient data, or preclinical animal or in vitro studies not directly generalizable to humans were excluded from the final analysis, except when cited selectively in the discussion to contextualize preclinical findings.

All retrieved articles were initially compiled, and duplicates were removed. Primary screening based on titles and abstracts was performed to exclude irrelevant studies. Subsequently, the full texts of the remaining articles were carefully reviewed, and the final selection was made according to the predefined inclusion and exclusion criteria.

A total of 42 records were identified during the initial search. Before the screening stage, 10 records were removed, including 4 duplicate records, 2 records identified as ineligible by automated screening tools, and 4 records excluded for other reasons. Subsequently, titles, abstracts, and full texts were evaluated for eligibility. Ultimately, 22 studies met the inclusion criteria and were included in the review, with all corresponding reports considered in the final analysis. The study selection process is illustrated in Figure 1.

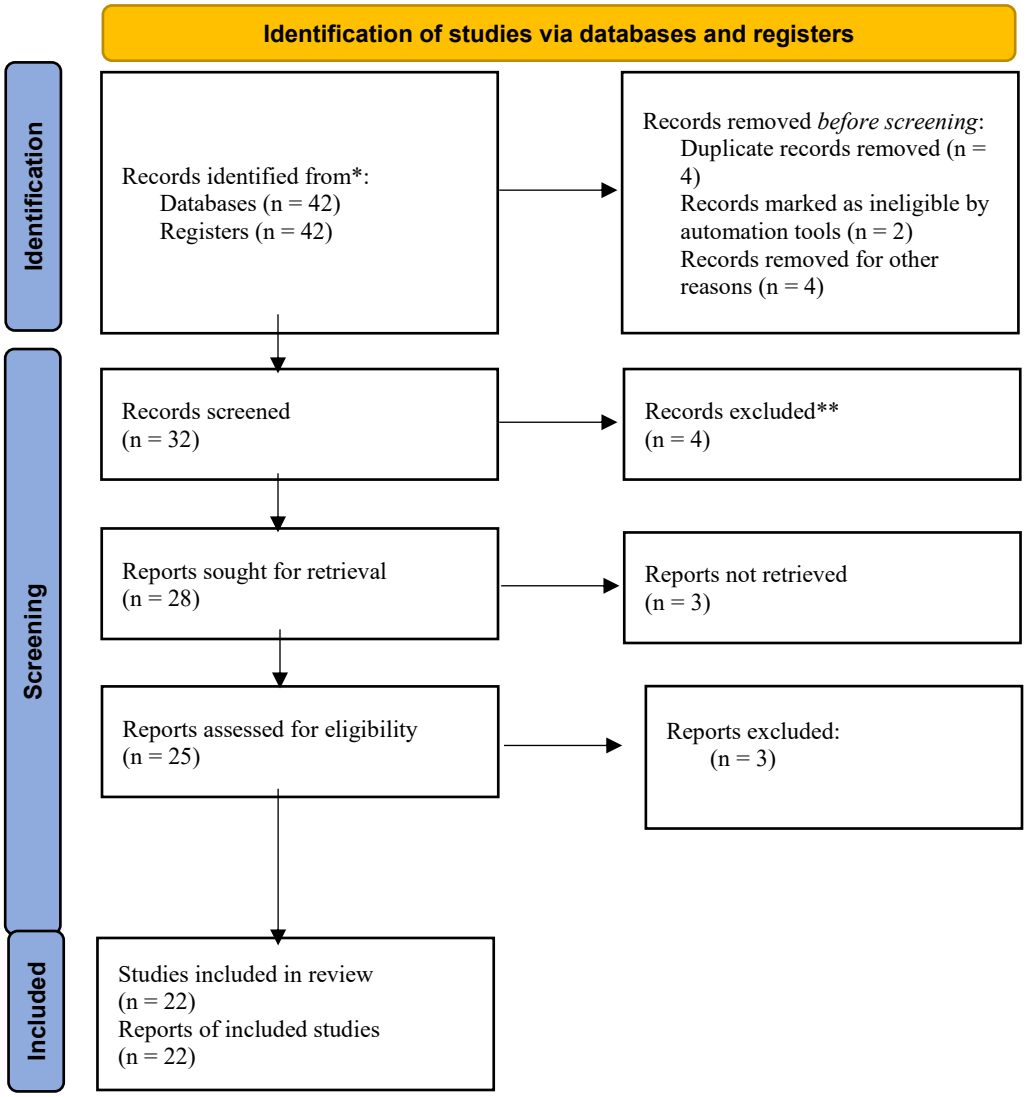

Figure 1. Flowchart of Search Strategy

Results

Evidence from both preclinical and clinical studies indicates that probiotics may modulate the progression of ovarian cancer through multiple mechanisms. Current findings suggest that specific probiotic strains are associated with inhibition of tumor cell proliferation and migration, induction of apoptosis, enhancement of immune responses, and attenuation of systemic inflammation. Additionally, modulation of the gut and reproductive tract microbiota has been reported in some studies to improve the efficacy of chemotherapy and reduce drug resistance. The data also underscore a significant association between microbial dysbiosis and disease prognosis.

A detailed summary of study characteristics including study type, probiotic strains, and reported outcomes is presented in Table 1.

Table 1: Characteristics of Selected Studies on the Role of Probiotics in Modulating Ovarian Cancer Progression

Year / Source	Model Type	Probiotic / Combination	Objective / Hypothesis	Key Findings	Mechanism / Pathway	Ref.
Zhou et al., 2024	Human	Bifidobacterium longum JBLC-141	Evaluate probiotic effects on paraneoplastic thrombocytosis	Reduced platelet elevation, improved coagulation, decreased inflammatory markers, microbiota modulation	Gut microbiota modulation impacting hemostatic parameters	[15]
Alipour et al., 2023	Human cell line	Lactobacillus rhamnosus	Assess effects on CAOV-4 cell death and gene expression	Downregulation of AKT/PI3K, upregulation of PTEN, inhibition of tumor growth	PI3K/AKT signaling and PTEN regulation	[16]
Sipos et al., 2021	Human cell line	Lactobacillus rhamnosus	Investigate probiotic effects on CAOV-4 cell death	AKT/PI3K suppression, PTEN upregulation, inhibition of proliferation	PI3K/AKT pathway and PTEN regulation	[17]
Hamade et al., 2024	Humanized mouse	Limosilactobacillus reuteri (LR-IL-22)	Evaluate intestinal radioprotection and survival	Increased survival, reduced tumor burden, CD8+ T cell activation, PD-L1 upregulation	Tumor microenvironment modulation, anti-tumor immunity	[18]
Blanco et al., 2025	Animal & human review	–	Explore microbiota role in ovarian cancer	Vaginal dysbiosis accelerates tumor growth; microbial interventions improve treatment response	DNA damage, inflammation, oncogenic metabolites	[19]
Mitra et al., 2024	Human review	Probiotics and prebiotics	Prevention of gynecologic cancers via microbiota modulation	Reduced Lactobacillus species associated with HPV and cervical dysplasia	Modulation of reproductive tract microbiota	[20]

Pourmollaei et al., 2023	Human cell line	Enterococcus faecium	Evaluate effects on CAOV-4 cells	Increased apoptosis, DNA damage, inhibition of cell growth	Regulation of pro- and anti-apoptotic genes	[21]
Chen et al., 2025	Human	–	Construct diagnostic microbiome model for EOC	Identified microbial markers and developed diagnostic model	PICRUSt2, WGCNA, LEfSe, LASSO, SVM	[22]
Fan et al., 2024	Human cell line	B. longum-EVs	Assess impact on carboplatin resistance	Reduced proliferation, increased apoptosis, enhanced sensitivity of resistant cells	Phosphorylation of p53 at Ser15	[23]
Zhou et al., 2019	Human	–	Analyze microbial diversity in ovarian tumors	Reduced microbial diversity; increased Proteobacteria/Firmicutes ratio	Modulation of fallopian tube microenvironment	[24]
Xie et al., 2024	Humanized mouse	Bifidobacterium animalis NCU-01 + Naringin	Evaluate cisplatin resistance	Reduced tumor size and CA125/HE4 markers; increased Bifidobacterium and Bacteroides	TLR4/NF-κB pathway, enhanced ZO-1 and occludin	[25]
Hamade et al., 2022	Mouse	L. reuteri (LR-IL-22)	Intestinal protection during radiotherapy	Improved gut barrier integrity, reduced cytokines, increased survival	Preservation of intestinal stem cells; reduced radiation-induced inflammation	[26]
Capozzi et al., 2024	Human meta-analysis	–	Correlate dysbiosis with ovarian cancer	No significant difference in dysbiosis prevalence observed	Further large-scale studies needed	[27]
Zhan et al., 2023	Mouse	Tripterygium glycosides + Cisplatin	Enhance anti-tumor effect and gut protection	Increased chemotherapy sensitivity, reduced intestinal injury	Restored gut microbial balance; protected intestinal barrier	[28]

Tong et al., 2020	Human	–	Assess gut microbiota changes after surgery and chemotherapy	Increased Bacteroides, Collinsella, Blautia; associated pathological features	Direct impact of surgery and chemotherapy on microbiota	[29]
Lin et al., 2022	Cell line & mouse	Naringenin	Inhibit epithelial ovarian cancer	Reduced proliferation and migration; decreased tumor volume	PI3K pathway inhibition; gut microbiota modulation	[30]
Okazawa-Sakai et al., 2024	Human	–	Gut microbiota and PARP inhibitor response	Increased Phascolarctobacterium associated with longer PFS in BRCA1/2-negative patients	Microbiota impact on therapy response	[31]
Chirakkara & Abraham, 2023	Cell & animal	Bacillus velezensis OM03 EPS	Assess ovarian cancer inhibition	Reduced proliferation, induced apoptosis, anti-angiogenic effects	Caspase-3 activation; DNA-dependent apoptosis	[32]
Wang et al., 2022	Mouse	Akkermansia + patient FMT	Suppress tumor progression via FMT	Reduced tumor growth; increased CD8+ T cell activity	Increased acetate production; T cell activation	[33]
Jacobson et al., 2021	Human	–	Gut and vaginal microbiome in cancer recurrence	Lactobacillus iners associated with disease-free status	Phylogenetic and inflammatory alterations	[34]
Dominique et al., 2024	Human & animal review	–	Gut microbiome in aging and ovarian cancer	Increased Proteobacteria and Escherichia; decreased SCFA	Microbiome impact on tumor microenvironment	[35]
D'Amico et al., 2021	Human	–	Microbiota dynamics during chemotherapy	Platinum-resistant patients: reduced diversity; increased Coriobacteriaceae and Bifidobacterium	Microbial diversity associated with treatment response	[36]

Huang et al., 2022	Cell line & human	Propionibacterium acnes	Role of intratumoral microbiota in EOC progression	Increased inflammation; Hedgehog pathway activation	Hedgehog pathway and inflammation	[37]

Despite the growing body of evidence supporting the role of probiotics and microbiota modulation in ovarian cancer, the quality and strength of current studies remain variable. Most human studies are limited by small sample sizes, heterogeneous patient populations, and short follow-up periods, which restrict the generalizability of their findings. In addition, a lack of standardization regarding probiotic strains, dosages, and routes of administration complicates the comparison of outcomes across studies. Preclinical investigations, including in vitro and animal models, often employ high concentrations of probiotics or engineered strains that may not fully reflect clinical scenarios. Consequently, although mechanistic insights such as modulation of the PI3K/AKT pathway, PTEN regulation, and immune system activation are compelling, their translation to human outcomes should be interpreted with caution. Future research should focus on well-designed randomized controlled trials with standardized interventions and extended follow-up to validate these findings and establish clinical efficacy.

Discussion

Ovarian cancer remains one of the most prevalent and lethal malignancies of the female reproductive system, frequently diagnosed at advanced stages. Its late detection, coupled with high rates of resistance to conventional therapies, underscores the urgent need for novel and effective therapeutic strategies [38].

Recently, growing attention has focused on the role of the microbiome and probiotics in ovarian cancer management. Preliminary evidence suggests that alterations in gut and vaginal microbiota can enhance host immune responses and improve the efficacy of standard treatments, including chemotherapy. When used as adjuncts, probiotics appear to inhibit tumor growth and mitigate treatment-related side effects, thereby improving patients' quality of life [39].

Ovarian cancer poses substantial clinical challenges. Resistance to standard therapies, severe adverse effects, and high recurrence rates highlight the need for exploring new therapeutic pathways. Emerging data indicate that gut and reproductive tract microbiota significantly influence disease progression and treatment response, presenting potential targets for innovative interventions.

Multiple studies have demonstrated that modulating gut microbiota with probiotics can improve coagulation and inflammatory parameters, reduce platelet counts, and favorably influence microbial composition [15]. These findings suggest that microbiota regulation functions not only as an anti-inflammatory mechanism but also primes the host environment through hemostatic modulation, enhancing responsiveness to systemic therapies.

At the molecular level, the PI3K/AKT pathway and PTEN regulation play pivotal roles in tumor suppression [16,17,30]. Downregulation of AKT/PI3K and upregulation of PTEN result in decreased cellular proliferation, induction of apoptosis, and inhibition of CAOV-4 and other ovarian tumor cell migration. Certain probiotic strains can modulate these oncogenic signaling pathways, contributing to anti-tumor effects.

Beyond signaling pathways, modulation of the tumor microenvironment and enhancement of anti-tumor immunity represent critical mechanisms. Preclinical models have shown that probiotic interventions increase CD8+ T cell activity and PD-L1 expression, indicating that microbiota regulation can stimulate anti-tumor immune responses, thereby reduce tumor burden and improve survival [18,33]. These observations highlight the complex, multi-level interaction between microbiota and anti-tumor immunity, which may also influence the efficacy of immunotherapy.

Furthermore, vaginal dysbiosis and depletion of beneficial Lactobacillus species have been linked to disease progression and cervical dysplasia [19,20,34]. Maintaining reproductive tract microbial health appears critical for treatment responsiveness and prognosis. Microbial shifts such as increased Proteobacteria and reduced short-chain fatty acid (SCFA) production [35] further demonstrate the microbiome's direct influence on the tumor microenvironment and metabolic pathways.

Studies also indicate that microbial interactions with standard therapies, including chemotherapy and surgery, can enhance drug sensitivity and protect against adverse effects such as intestinal barrier disruption [28,29]. These findings reinforce the role of the microbiota in modulating the impact of invasive treatments and supporting patient health.

From a predictive and diagnostic standpoint, identifying microbial biomarkers and developing diagnostic models using tools such as PICRUSt2, WGCNA, LEfSe, and machine learning algorithms [22] holds promise for personalized therapy and predicting patient responses. This approach may enable more targeted treatment selection and help overcome drug resistance.

Overall, the evidence indicates that the microbiota functions not only as an adjunct to therapy but also as an independent regulator of tumor growth, apoptosis induction, angiogenesis inhibition, and immune modulation [21,32,36,37]. Consequently, integrating standard therapies with microbiota-targeted or probiotic interventions may provide an effective

complementary approach to improving outcomes in ovarian cancer patients.

Studies indicate that probiotics can exert antitumor effects through multiple mechanistic pathways, which can be broadly classified into four main domains. At the cellular level, probiotics inhibit cancer cell proliferation and induce apoptosis, thereby limiting tumor growth. These effects have been consistently observed in studies utilizing CAOV-4 cell lines and animal models, demonstrating the capacity of probiotics to reduce cell viability and promote programmed cell death [40].

At the molecular level, probiotics modulate critical signaling pathways, including inhibition of PI3K/AKT and activation of tumor suppressors such as PTEN and p53. These molecular alterations result in decreased cell proliferation, induction of cell cycle arrest, and enhanced sensitivity to chemotherapeutic agents, thereby playing a pivotal role in regulating cancer cell growth and survival [41].

From an immunological perspective, probiotics enhance antitumor immune responses by promoting $CD8^+$ T cell activity and modulating the expression of PD-L1 and other pro-inflammatory pathways. These immunomodulatory effects contribute to reduced tumor burden and improved responses to conventional therapies, including chemotherapy and immunotherapy [40,41].

Within the microbiome–metabolite axis, probiotics restore microbial balance in the gut and reproductive tract, stimulate the production of beneficial metabolites such as short-chain fatty acids (SCFAs), and reduce dysbiosis and tumor-promoting metabolites. These alterations not only foster a host-supportive microbial environment but also interact with molecular and immune pathways to suppress tumor growth and enhance therapeutic responsiveness [40,41].

Overall, the integration of cellular, molecular, immunological, and microbiome-mediated effects indicates that probiotics establish a multi-level mechanistic framework. This framework may serve as a complementary strategy in ovarian cancer management and provide a foundation for guiding future clinical investigations [40,41].

Some preclinical studies, including cellular and animal experiments, have demonstrated promising mechanistic and therapeutic effects; however, these findings cannot be directly extrapolated to clinical practice. The use of high concentrations or engineered probiotic strains in animal models may not accurately reflect real-world patient conditions. Consequently, although modulation of signaling pathways such as PI3K/AKT and PTEN, along with immune system activation, provides valuable mechanistic insights, translating these results to humans requires caution and further clinical investigation. Future research should focus on well-designed randomized clinical trials with standardized interventions and extended follow-up periods to validate the clinical effects of probiotics and microbiota modulation in ovarian cancer and address current limitations.

While probiotics are generally regarded as safe, potential risks must be acknowledged, particularly in immunocompromised patients, where opportunistic infections may occur. Differences between oral probiotic supplementation and targeted microbiome-based interventions may also influence efficacy and safety profiles. Therefore, although preclinical and early clinical data are encouraging, careful monitoring and well-designed clinical trials are essential to fully evaluate the safety and therapeutic potential of probiotics in patients with ovarian cancer [42–44]. Women's health and the study of gynecologic cancers are critical for early detection, effective prevention, and reduction of disease-related mortality [45–49]. Consequently, the implementation of immunotherapeutic approaches appears to be essential.

Conclusion

Probiotics represent a safe and promising adjunct in the management of ovarian cancer. These beneficial microorganisms may enhance antitumor immune responses by stimulating $CD8^+$ T cell activity and modulating PD-L1 expression. By supporting intestinal barrier integrity and reducing systemic inflammation, probiotics can help mitigate some of the adverse effects associated with conventional therapies. They may also influence key molecular pathways involved in cancer progression, including PI3K/AKT and PTEN, potentially contributing to reduced tumor cell proliferation and migration. Furthermore, modulation of gut and reproductive tract microbiota can decrease inflammation and oncogenic metabolites while improving sensitivity to chemotherapeutic agents. The identification of microbial biomarkers and predictive models may further inform personalized treatment strategies. Nevertheless, given the current limitations of clinical data, probiotics should be regarded as a complementary approach rather than a standalone therapy, and additional well-designed clinical trials are required to confirm their efficacy in patients with ovarian cancer.

Declaration

Conflict of Interest

The authors declare that they have no competing interests relevant to the content of this article.

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