Gut microbiota as a multifaceted modulator of prostate cancer: Mechanistic insights, therapeutic opportunities and clinical challenges (Review)

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Abstract. Prostate cancer (PCa) ranks among the most prevalent malignancies among men worldwide, emphasizing the need for innovative therapeutic strategies. Studies have suggested that the gut microbiota may markedly influence PCa pathogenesis through mechanisms such as immunomodulation and metabolic regulation. The present review systematically examined the composition and diversity of the gut microbiota, highlighted clinical evidence linking microbial dysbiosis to PCa risk and examined discrepancies in existing research. Additionally, it explored the therapeutic potential of microbiota modulation, through the use of probiotics and dietary interventions, in enhancing treatment responses. Despite emerging insights, challenges persist, including methodological variations and patient heterogeneity. The present review highlighted the need for further research to elucidate the role of the gut microbiota and support the development of personalized approaches for PCa management. The novelty of this work lay in its comprehensive synthesis of current evidence on the role of the gut microbiota in PCa, identification of gaps in existing research and proposal of future directions to advance our understanding of this emerging field.

Contents

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1. Introduction

Prostate cancer (PCa) is one of the most prevalent malignancies among men worldwide, making it a significant public health concern (1). According to the Global Cancer Observatory, PCa accounted for ~1.4 million new cases and 375,000 deaths in 2020, ranking it as the second leading cause of cancer-related mortality in men (1). The incidence of PCa varies by geographic region, with higher rates observed in North America and Europe compared with Asia and Africa (2). Despite advances in early detection and treatment strategies, such as radical prostatectomy and androgen deprivation therapy (ADT), the pathophysiology of PCa remains complex and multifactorial and a deeper understanding of its underlying mechanisms is needed to improve therapeutic outcomes (3).

Recent studies have illuminated the importance of the gut microbiota in human health, highlighting its role in various physiological and pathological processes (4,5). The gut microbiota, defined as the collective community of microorganisms residing in the gastrointestinal tract, includes bacteria, archaea, viruses and fungi (6). A diverse gut microbiota plays a crucial role in the synthesis of nutrients, metabolism of drugs, regulation of immune responses and protection against pathogenic organisms (7). Dysbiosis, or an imbalance in gut microbiota composition, has been implicated in a wide range of diseases, including obesity, diabetes, inflammatory bowel disease and even various forms of cancer (8). The gut-brain and gut-liver axes further underscore the systemic effects of the microbiota, suggesting that microbial composition can influence distant organ systems (9,10).

The rationale for exploring the role of gut microbiota in PCa stems from emerging evidence linking gut health with cancer risk and progression (11). Several studies have

identified a distinctive microbial signature in patients with PCa compared with healthy individuals, suggesting that alterations in gut microbiota may influence cancer development (12,13). The mechanisms through which gut microbiota may exert their influence on prostate carcinogenesis are multifaceted, encompassing modulation of local and systemic inflammation, alteration of hormone metabolism and impacts on drug metabolism and efficacy (14). Given that inflammation and hormonal factors are well-established contributors to PCa development, understanding how microbial populations affect these pathways is critical (15,16).

Furthermore, the interplay between diet, lifestyle factors and the gut microbiota presents an intriguing opportunity for research (17). Dietary patterns have been shown to markedly alter gut microbiota composition, with Western diets, characterized by high fat and low fiber intake, being associated with increased dysbiosis (18). This suggests a potential link between dietary habits, gut health and PCa risk that warrants further investigation. Additionally, the growing interest in microbiome-targeted therapies, such as probiotics and dietary interventions, raises the prospect of novel prevention and treatment strategies in PCa (19).

Despite the promising associations established between gut microbiota and PCa, the field remains nascent, with significant gaps in our understanding. Studies on this topic often present conflicting results, stemming from variations in methodology, sample sizes and population diversity (20). Some research suggests specific microbial taxa may be associated with increased cancer risk, while others highlight protective microbial profiles. Such discrepancies highlight the need for a critical appraisal of existing literature to elucidate consistent findings and bounding contradictions (21). The present review aimed to synthesize the current evidence and propose directions for future research, with the hope of fostering an improved understanding of how gut microbiota may serve as both a modulator of PCa risk and a potential target for therapeutic intervention.

2. Gut microbiota and cancer

Description of gut microbiota composition and diversity. The gut microbiota is an intricate consortium of microorganisms, including bacteria, archaea, fungi and virus, that inhabit the gastrointestinal tract (22) (Fig. 1). The human gut harbors ~100 trillion microbial cells, outnumbering human cells by a factor of ten (23). These microorganisms predominantly belong to two major phyla: Firmicutes and Bacteroidetes, along with smaller representations from Actinobacteria, Proteobacteria and Verrucomicrobia (23). The composition and diversity of the gut microbiota can be influenced by various factors, including diet, age, genetics and antibiotic use (24).

A diverse gut microbiota is indicative of a healthy gastrointestinal ecosystem, playing a crucial role in nutrient metabolism, barrier integrity and immune system function (25). Dysbiosis, or an imbalance in microbiota composition, has been associated with various diseases, including inflammatory bowel disease, obesity and cancer (8,26,27). Recent advances in high-throughput sequencing technologies have enabled a more nuanced understanding of microbial communities and have revealed specific microbial signatures associated with specific health conditions, including malignancies (28).

Variability in gut microbiota profiles has been observed across populations, suggesting environmental and lifestyle factors play significant roles in shaping these communities (29). For instance, populations consuming a Western diet rich in fats and sugars often exhibit decreased microbial diversity, which has been linked to increased cancer risk (30,31). Comparatively, traditional diets that emphasize plant-based foods are associated with a higher diversity of beneficial gut microbes, which may provide protective effects against various cancers (32).

Mechanisms by which gut microbiota may influence cancer pathogenesis. The influence of gut microbiota on cancer pathogenesis occurs through several mechanisms, which can markedly affect the initiation, promotion and progression of tumors (33). Among these mechanisms are immunomodulation, metabolic processes and the production of bioactive compounds (33).

Immunomodulation: The gut microbiota plays a pivotal role in shaping the immune system, promoting both innate and adaptive immune responses (34). Commensal bacteria stimulate the production of immune cells, including regulatory T cells (Tregs) and dendritic cells, which in turn influence systemic immune responses (34). Dysbiosis can lead to an altered immune landscape, characterized by chronic inflammation, which is recognized as a risk factor for cancer development (35). For instance, chronic inflammation driven by microbial imbalances can result in cellular stress, DNA damage and ultimately tumorigenesis (35) (Fig. 1).

Metabolism of xenobiotics and nutrients: The gut microbiota is crucial in metabolizing dietary and environmental xenobiotics, converting them into bioactive compounds that can influence cancer risk (7). For example, certain gut bacteria can metabolize dietary fiber into short-chain fatty acids (SCFAs), such as butyrate, which possesses anti-cancer properties (36). Butyrate has been shown to inhibit tumor cell proliferation and promote apoptosis in colorectal cancer models (37). Conversely, the metabolism of certain amines and phenolic compounds by gut microbes can yield carcinogenic metabolites, increasing cancer susceptibility (38) (Fig. 1).

Alteration of Gut Barrier Function: A healthy gut microbiota helps maintain intestinal barrier integrity, preventing translocation of pathogens and toxins into the systemic circulation (39). Dysbiosis can disrupt the epithelial barrier, allowing bacterial endotoxins to enter the bloodstream and provoke systemic inflammation, contributing to cancer risk (40) (Fig. 1).

The association of gut microbiota with tumors, including PCa. Significant evidence suggests that gut microbiota is implicated in the pathogenesis of various cancers, including colorectal, breast and liver cancers (41). A notable study by Kang *et al* (42) observed distinct microbial profiles in colorectal cancer patients characterized by a reduction in butyrate-producing bacteria. Similarly, research has indicated that specific phylotypes, such as *Fusobacterium nucleatum*, are enriched in colorectal tumors and may promote tumor growth through inflammatory pathways (43). In the context of breast cancer, several studies have reported associations between gut microbiota composition and tumor development. Caleça *et al* (44) found that women with breast cancer

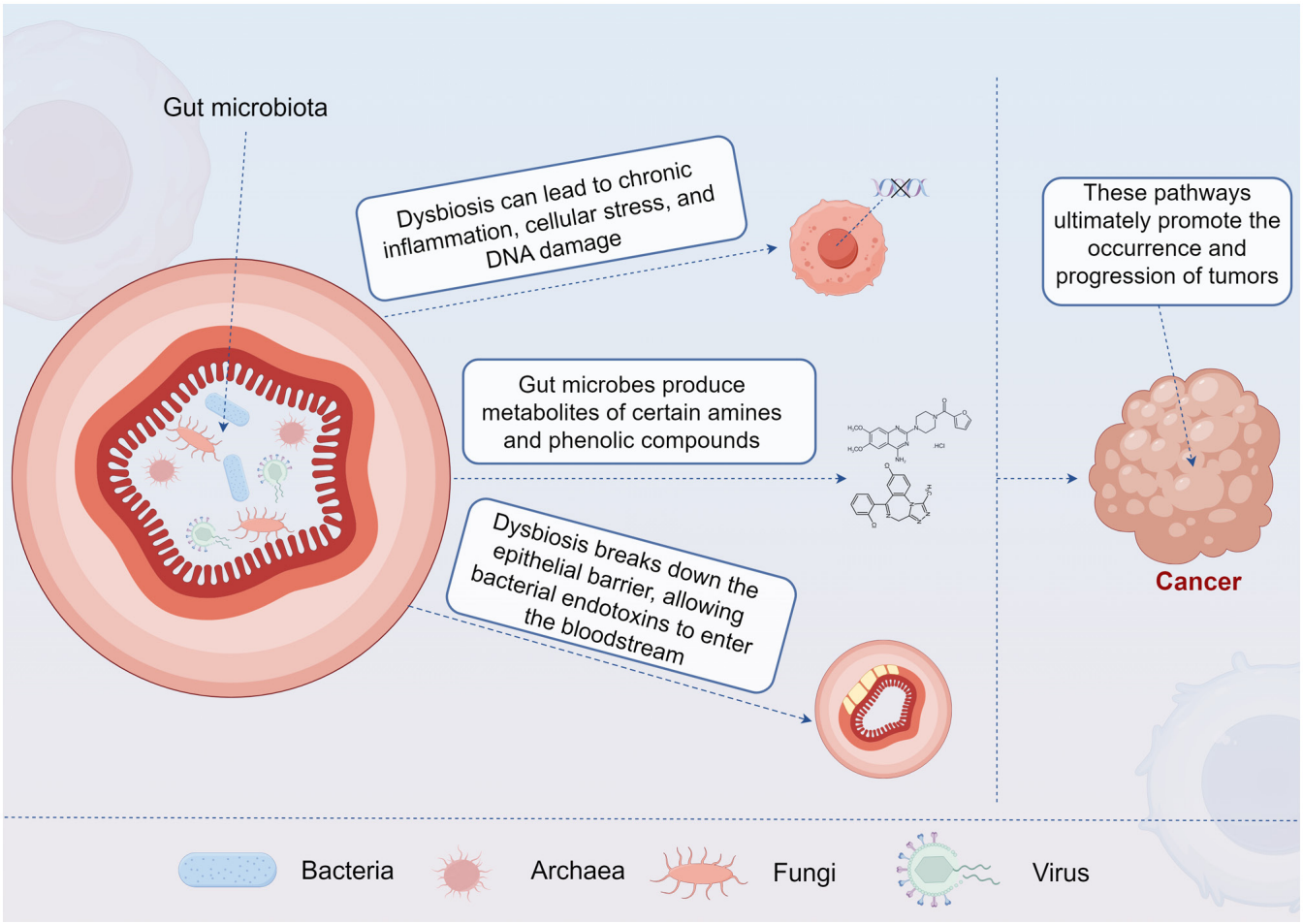

Figure 1. Composition of intestinal microbiota and its mechanism of action on tumors (generated with Figdraw; www.figdraw.com; ID: AUIUR55151).

exhibited specific dysbiotic features compared with healthy controls. Furthermore, gut microbiota modulation through dietary interventions showed promise in altering the risk of breast cancer through immune system reprogramming (45).

The relevance of gut microbiota to PCa is a burgeoning area of research. Wang *et al* (46) reported a significant correlation between gut microbiota composition and PCa risk, indicating that distinctive microbial communities may be associated with tumor presence. Notably, studies employing fecal microbiota transplantation have highlighted the potential for gut microbiota to influence host tumor immunology and responses to therapeutic interventions (47,48). Despite these findings, there are inconsistencies and limitations in the current literature linking gut microbiota to PCa. Some studies report significant associations, while others fail to demonstrate a clear connection, suggesting that variations in methodology, sample size and environmental factors may influence outcomes (49,50). Furthermore, the geographic and dietary contexts in which studies are conducted may contribute to discrepancies in microbial composition and cancer susceptibility (51,52).

3. Clinical evidence linking gut microbiota to PCa

Accumulating clinical evidence supports the association between gut microbiota and PCa pathogenesis and progression (53-63). Key studies have identified distinct microbial signatures in patients with PCa compared with healthy controls, with variations observed across disease stages and treatment modalities. These findings are summarized in Table I, which highlights study designs, patient cohorts and principal outcomes.

The role of the gut microbiota in PCa pathology has gained traction, as illustrated by Golombos *et al* (53) in their prospective pilot study. The authors observed significant differences in gut microbiota composition among men diagnosed with PCa compared with healthy controls, highlighting alterations in specific microbial profiles that may be relevant to cancer development (53). However, the small sample size and the lack of diverse demographics limit the generalizability of these findings. In another study conducted by Liu and Jiang (54), compositional differences were noted between hormone-sensitive and castration-resistant patients with PCa. This study found that specific microbial taxa were enriched in patients with castration-resistant disease, suggesting that gut microbiota may influence disease progression and therapeutic resistance. However, the design was retrospective and causality could not be firmly established.

A randomized controlled trial has also provided valuable insights. Newton *et al* (55) explored the effect of exercise on gut microbiota composition in individuals undergoing ADT for PCa. The authors reported that the exercise intervention led to modifications in the gut microbiota, which may correlate with

Table I. Clinical studies of gut microbiota and PCa.

First author/s, year	Study type	Number of patients	Patient type	Findings	(Refs.)
Golombos *et al*, 2018	Prospective pilot study	32	Men diagnosed with PCa vs. healthy controls	Significant differences in gut microbiota composition	(53)
Liu and Jiang, 2020	Retrospective study	21	Hormone-sensitive vs. castration-resistant patients with PCa	Compositional differences with enrichment in specific taxa in castration-resistant disease	(54)
Newton *et al*, 2019	Randomized controlled trial	60	Individuals undergoing ADT for PCa	Exercise intervention led to modifications in the gut microbiota	(55)
Matsushita *et al*, 2021	Case-control study	152	Patients with high-Gleason PCa	Unique microbial signature associated with aggressive cancer phenotypes	(56)
Li *et al*, 2021	Cross-sectional study	86	Patients with PCa undergoing prostatectomy or ADT	Significant changes in gut microbiota profiles with more pronounced dysbiosis in ADT patients	(57)
Takezawa *et al*, 2021	Case-control study	128	Patients with prostate enlargement	Potential association between gut microbiota composition and urological conditions	(58)
Matsushita *et al*, 2022	Cohort study	54	Elderly men with PCa	Firmicutes correlations with blood testosterone levels	(59)
Fernandes *et al*, 2022	Pilot case series study	5	Patients with PCa treated with Radium-223	Significant shifts in microbial populations post-treatment	(60)
Huang *et al*, 2024	Systematic review and meta-analysis	442	Patients with PCa vs. healthy individuals	Significant differences in gut microbiota profiles	(61)
Smith *et al*, 2021	Randomised controlled trial	44	Breast and PCa cases vs. matched cancer-free controls	Gut microbial differences	(62)
Reichard *et al*, 2022	Prospective analysis of a cohort	692	Patients at risk of lethal PCa	Gut microbiota-dependent metabolic pathways and risk of lethal PCa	(63)

PCa, prostate cancer; ADT, androgen deprivation therapy.

improved patient outcomes. While this study provides promising evidence on lifestyle interventions, the results must be interpreted with caution due to potential confounding factors related to exercise types and patient adherence. Moreover, Matsushita *et al* (56) assessed gut microbiota in relation to high-Gleason PCa. The authors identified a unique microbial signature associated with aggressive cancer phenotypes, thus emphasizing the potential of microbiota profiling for risk stratification in clinical practice. The findings contribute to our understanding but warrant further validation in larger cohorts.

Li *et al* (57) conducted a cross-sectional study among patients with PCa undergoing prostatectomy or ADT, demonstrating significant changes in gut microbiota profiles. The study revealed that patients undergoing ADT experienced more pronounced dysbiosis, which correlated with therapy outcomes. While these findings are useful, the cross-sectional nature of the study limits causal inferences. Takezawa *et al* (58) also investigated the Firmicutes/Bacteroidetes ratio in connection with prostate enlargement, establishing a potential association between gut microbiota composition and urological conditions. However, the specific relevance to cancer remains unclear and needs to be contextualized within a broader oncological framework.

Emerging longitudinal studies have further illuminated the relationship between gut microbiota and PCa. Matsushita *et al* (59) conducted a detailed examination of firmicutes correlations and blood testosterone levels in elderly men with PCa, supporting the concept that microbiota could influence hormonal pathways that are critical in cancer progression. While insightful, the study's retrospective nature poses challenges to establishing direct causative relationships. The case series exploring the effects of Radium-223 on gut

microbiota reported significant shifts in microbial populations post-treatment, suggesting that certain therapies might modulate the microbiome, which in turn could influence cancer dynamics (60). The limited sample size and lack of controls temper the broader applicability of these findings, highlighting the need for further robust studies.

A systematic review and meta-analysis by Huang *et al* (61) synthesized data from various studies, confirming that significant differences exist in gut microbiota profiles between patients with PCa and healthy individuals. This comprehensive review underscores the reproducibility of observed dysbiosis across different populations and study designs. Nevertheless, the heterogeneity of study methodologies and microbiota analyses complicates direct comparisons. Moreover, a Mendelian randomization study by Wang *et al* (46) suggested a causal relationship between gut microbiota and PCa. The authors' findings advocate for the gut-prostate axis by demonstrating potential microbiome-driven mechanisms influencing prostate disease pathology. This strengthens the biologic plausibility of the gut microbiota's role in PCa, although the models require rigorous validation. In addition, prospective cohort analyses have shown that gut microbiome-dependent metabolic pathways may be associated with the risk of developing lethal prostate cancer, further supporting the clinical relevance of microbial metabolism in PCa pathogenesis (63).

In summary, clinical evidence consistently reports a state of gut microbiota dysbiosis in patients with PCa compared with healthy controls (53,61). Key findings include distinct microbial signatures associated with PCa presence (53,56), differences between disease states such as hormone-sensitive and castration-resistant PCa (54) and modulations induced by therapies such as ADT (57) or Radium-223 (60). Furthermore, interventions such as exercise have been shown to alter the gut microbiota in patients with PCa (55). Despite this accumulation of evidence, significant inconsistencies remain regarding the specific microbial taxa associated with increased or decreased risk. For instance, the roles of Bacteroides, Streptococcus and Faecalibacterium prausnitzii, as well as the Firmicutes/Bacteroidetes ratio, are not consistently reported across studies (58,62,64,65). These discrepancies are likely attributable to methodological variations (such as sequencing techniques, bioinformatic pipelines) and profound inter-individual and geographic heterogeneity in microbiome composition (49,51). Therefore, while a consensus confirms the involvement of gut microbiota in PCa, future multi-center studies with standardized protocols are essential to identify robust, generalizable microbial signatures for clinical application.

4. Mechanisms of action

The gut microbiota influences PCa through multiple interconnected mechanisms, including metabolic regulation, immune modulation and hormonal signaling. Major pathways involve microbial metabolites such as short-chain fatty acids (SCFAs), inflammation-related axes (such as NF-κB-IL6-STAT3) and androgen metabolism (66), and key mechanistic pathways are illustrated in Fig. 2. A summary of these mechanisms and supporting studies is provided in Table II.

Dysbiosis and PCa progression. A growing body of evidence suggests that alterations in gut microbiota composition, referred to as dysbiosis, are closely associated with PCa progression (61,67). Liu *et al* (67) found that specific taxa, when disrupted, lead to increased levels of LPCAT1, a lysophosphatidylcholine acyltransferase involved in membrane repair, which promotes cancer cell survival and progression. In this context, the study highlights a critical intersection between microbial metabolism and cancer biology. Another study by Matsushita *et al* (68) emphasizes the role of SCFAs derived from gut microbiota in promoting PCa growth. The authors' research revealed that SCFAs activate the insulin-such as growth factor 1 (IGF1) signaling pathway, which is well-known for its role in cell proliferation and survival . Hence, the microbial production of SCFAs offers a potential oncogenic pathway that merits further exploration.

Androgen biosynthesis and resistance mechanisms. Studies have illuminated the role of gut microbiota in modulating androgen biosynthesis, a crucial factor in PCa development. Pernigoni *et al* (69) demonstrated that commensal bacteria could promote endocrine resistance by altering androgen synthesis pathways, potentially leading to treatment resistance in PCa. This finding underlines the necessity of considering microbial influences in both hormonal regulation and therapeutic strategies against PCa. Furthermore, Matsushita *et al* (70) also reported that high-fat diets, which can alter gut microbiota composition, enhance histamine signaling and foster an environment conducive to PCa progression. The dual role of diet and gut microbiota in cancer dynamics highlights the complexity of interactions and the importance of holistic approaches in cancer management.

Inflammatory pathways involved in PCa progression. Dysbiosis has been linked to chronic inflammation, which is a precursor in a number of cancers, including PCa (71). Zhong *et al* (72) established that gut microbiota dysbiosis activates the NF-κB-IL6-STAT3 axis, promoting not only PCa progression but also docetaxel resistance. This finding suggests that therapies targeting the gut microbiota could enhance the efficacy of conventional treatments by modulating the inflammatory milieu associated with PCa. Moreover, Bui *et al* (73) highlighted *Clostridium scindens* metabolites as triggers of PCa progression through androgen receptor signaling. This indicates that specific microbial metabolites can directly affect cancer biology, suggesting possible intervention strategies aimed at microbial pathway manipulation.

Autophagy and immune response modulation. Gut microbiota-derived molecules have also been implicated in regulating autophagy and immune responses in PCa. Liu *et al* (74) reported that SCFAs promote cancer cell autophagy and the polarization of M2 macrophages, facilitating a tumor-promoting environment. As immune evasion is a critical hallmark of cancer, understanding how gut microbiota influences immune modulation could pave the way for innovative therapeutic strategies (34). In a related study, Hsia *et al* (75) demonstrated that butyrate, a major SCFAs, increases methylglyoxal production via the JAK2/Stat3/Nrf2/Glo1 pathway in castration-resistant

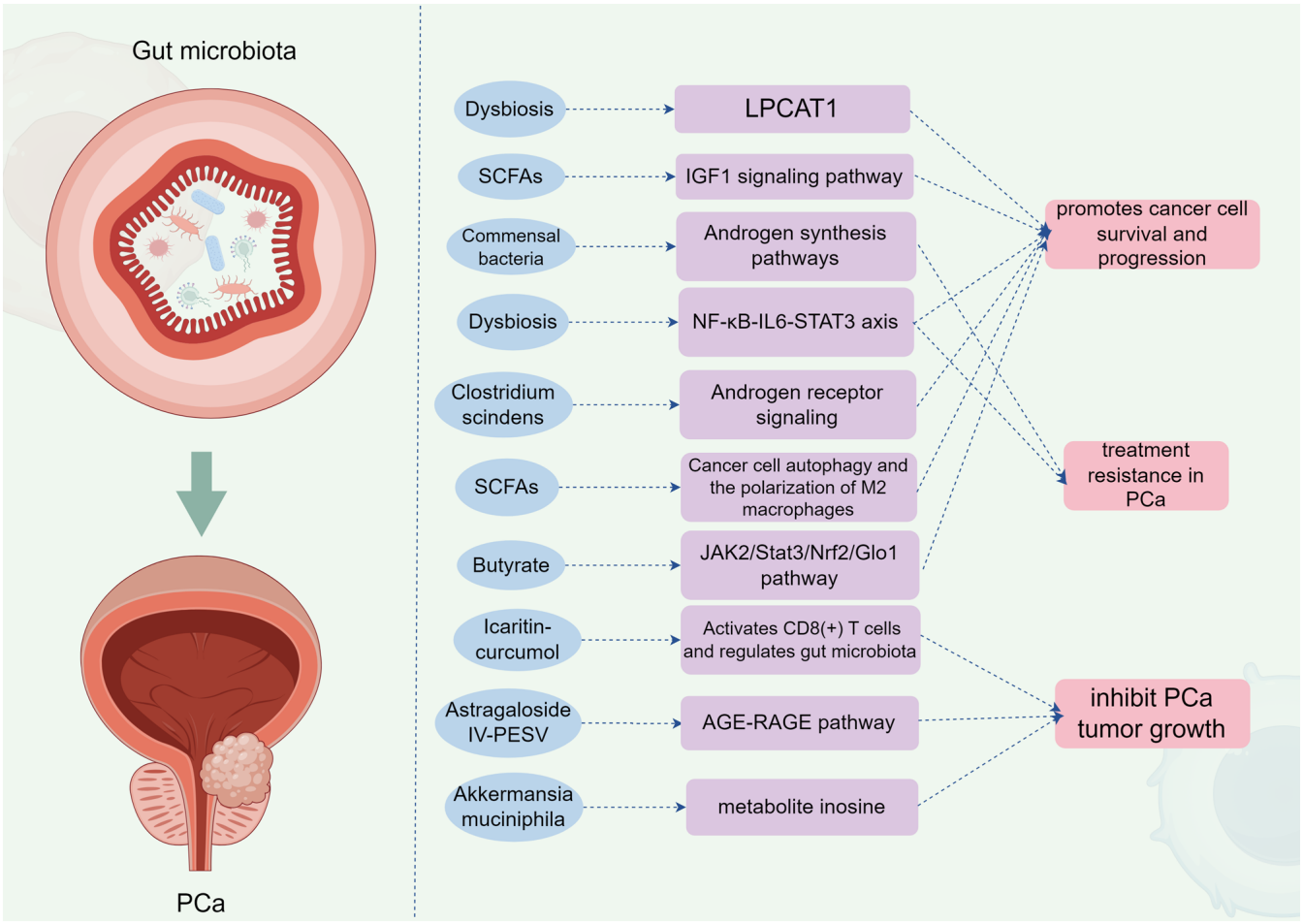

Figure 2. Mechanism of action of gut microbiota on prostate cancer (generated with Figdraw; www.figdraw.com; ID: RWTIA8dd77). SCFAs, short-chain fatty acids; LPCAT1, lysophosphatidylcholine acyltransferase; IGF1, insulin-like growth factor 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL-6, interleukin-6; STAT3, signal transducer and activator of transcription 3; JAK2, Janus kinase 2; Nrf2, nuclear factor erythroid 2-related factor 2; Glo1, glyoxalase 1; LPCAT1, lysophosphatidylcholine acyltransferase 1; AGE, advanced glycation end-product; RAGE, receptor for advanced glycation end-products; PCa, prostate cancer; CRPC, castration-resistant prostate cancer.

PCa cells, further implicating metabolic interplay in cancer progression. These findings emphasize the multifaceted roles of gut-derived metabolites in shaping tumor biology.

Mechanisms of cancer suppression via gut microbiota. Notably, research has also shown that certain natural compounds can restore gut microbiota homeostasis, potentially suppressing PCa progression (61). Xu *et al* (76) explored the action of Icaritin-curcumol, which activates CD8 (+) T cells and regulates gut microbiota, demonstrating a dual effect on immune enhancement and cancer suppression. This highlights promising avenues for therapeutic strategies that incorporate microbiota modulation alongside conventional treatments. Furthermore, You *et al* (77) presented evidence indicating that Astragaloside IV-PESV can inhibit PCa tumor growth through gut microbiota restoration and metabolic homeostasis, which is mediated via the AGE-RAGE pathway. Such findings contribute to a growing body of literature supporting the significance of gut microbiota in cancer therapeutics. Lastly, Yu *et al* (78) investigated *Akkermansia muciniphila* and its metabolite inosine, which inhibits castration resistance in PCa. This research reinforces the notion that specific microbial taxa could serve as therapeutic targets or biomarkers, further integrating gut microbiota research into PCa clinical practice.

The intricate interplay between gut microbiota and PCa progression underscores the necessity for further research in this burgeoning field (79). Studies consistently highlight that dysbiosis not only contributes to the pathogenesis of PCa but also influences the efficacy of various treatment modalities (52,72). As we continue to unravel these complex relationships, it is vital to incorporate gut microbiota considerations into PCa management strategies, paving the way for personalized therapeutic approaches that target the microbiome for improved outcomes. The ongoing exploration of microbial metabolites, signaling pathways and dietary factors will undoubtedly provide new insights into the mechanisms of PCa progression and resistance, ultimately benefiting patient care and treatment efficacy.

5. Microbiota as a therapeutic target

Modulating gut microbiota presents a promising avenue for influencing PCa pathogenesis and treatment outcomes (11). Interventions, including probiotics, prebiotics and dietary changes, aim to restore microbiota balance and enhance

Table II. Key mechanisms of gut microbiota influence on PCa progression.

First author/s, year	Mechanism category	Key elements/ microbial factors	Proposed effect on PCa	(Refs.)
Matsushita *et al*, 2021; Liu *et al*, 2023	Metabolic Regulation	SCFAs	Activate IGF1 signaling, promoting cell proliferation and survival. Promote autophagy and M2 macrophage polarization, facilitating a tumor-promoting environment.	(68,74)
Hsia *et al*, 2024	Metabolic Regulation	Microbial modulation of methylglyoxal	Butyrate increases methylglyoxal production via JAK2/Stat3/Nrf2/Glo1 pathway in CRPC.	(75)
Zhong *et al*, 2022	Immune Modulation and Inflammation	NF-κB-IL6-STAT3 axis activation	Dysbiosis activates this inflammatory axis, promoting PCa progression and docetaxel resistance.	(72)
Xu *et al*, 2024	Immune Modulation and Inflammation	CD8 (+) T cell activation	Compounds such as Icaritin-curcumol can activate CD8 (+) T cells and regulate gut microbiota, suppressing cancer.	(76)
Pernigoni *et al*, 2021	Hormonal Signaling	Androgen biosynthesis	Commensal bacteria can alter androgen synthesis pathways, promoting endocrine resistance.	(69)
Bui *et al*, 2023	Hormonal Signaling	Androgen receptor signaling	Metabolites from *Clostridium scindens* can trigger PCa progression via androgen receptor signaling.	(73)
Liu *et al*, 2021	Other Pathways	LPCAT1 upregulation	Gut dysbiosis can increase LPCAT1 expression, enhancing DNA repair pathways and promoting cancer cell survival.	(67)
You *et al*, 2024	Other Pathways	AGE-RAGE pathway	Restoration of gut microbiota and metabolic homeostasis via this pathway can inhibit tumor growth (such as Astragaloside IV-PESV).	(77)
Yu *et al*, 2024	Other Pathways	Bacterial metabolites (e.g., Inosine)	*Akkermansia muciniphila* metabolite inosine inhibits castration resistance.	(78)

PCa, prostate cancer; CRPC, castration-resistant prostate cancer; ADT, androgen-deprivation therapy; SCFAs, short-chain fatty acids; IGF1, insulin-like growth factor 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL-6, interleukin-6; STAT3, signal transducer and activator of transcription 3; JAK2, Janus kinase 2; Nrf2, nuclear factor erythroid 2-related factor 2; Glo1, glyoxalase 1; LPCAT1, lysophosphatidylcholine acyltransferase 1; RAGE, receptor for advanced glycation end-products.

immune function (19). However, the variability in individual microbiome compositions and the specificities of intervention effects necessitate careful evaluation of available studies and clinical trials to establish effective and personalized therapeutic strategies (52).

Role of microbiota in modulating responses to PCa treatments. Emerging evidence suggests that the composition of gut microbiota can markedly influence the effectiveness of various PCa treatments, specifically immunotherapies and chemotherapies (52,72). For instance, it has been shown that specific gut bacteria can enhance the efficacy of immune checkpoint inhibitors by modulating systemic immune responses (80). A study found that patients with colorectal cancer who had a higher abundance of certain gut bacteria experienced improved responses to immunotherapy, raising the possibility that similar principles could apply to PCa treatment (81). Conversely, dysbiosis may lead to decreased effectiveness of chemotherapy. Antibiotic exposure during treatment can disrupt microbiota balance, potentially diminishing therapeutic outcomes and increasing susceptibility to adverse effects (67). Thus, understanding how gut microbiota interact with therapeutic modalities could inform approaches to enhance treatment efficacy and minimize toxicity.

Exploration of potential interventions targeting gut microbiota. Probiotics, defined as live microorganisms that confer health benefits, have been shown to restore gut microbiota balance (82). Specific strains, such as *Lactobacillus rhamnosus*, have been demonstrated to enhance immune modulation, which may inhibit tumor growth and progression. However, the efficacy of probiotics can vary markedly by strain and individual response due to unique host microbiota compositions (83). For instance, while certain strains may exert beneficial effects, others may not confer the same advantages, raising questions about strain specificity and the need for personalized approaches (84).

Prebiotics, which are non-digestible food components that promote beneficial bacteria growth, have also gained attention (85). They can selectively increase populations of SCFAs-producing bacteria, such as *Faecalibacterium*, linked to anti-inflammatory properties (86). Dietary modifications focused on increasing fiber intake may support these beneficial communities while simultaneously mitigating dysbiosis and inflammation (87). Nevertheless, the challenge lies in establishing standardized guidelines on effective prebiotic intake, given the variability in individual gut microbiota responses.

Further, dietary interventions are increasingly seen as viable approaches to alter gut microbiota (88). Studies suggest that Mediterranean diets rich in fruits, vegetables and whole grains can enhance microbial diversity and reduce cancer progression risk (89,90). However, a number of these studies are observational and require causal evidence to substantiate claims regarding dietary impact on PCa outcomes.

Emerging clinical trials and studies. The gut microbiota has emerged as a potential therapeutic target in the management of PCa, with recent studies highlighting its role in disease progression and response to treatment (91). The modulation of gut microbiota through dietary interventions, prebiotics, probiotics and fecal microbiota transplantation (FMT) has shown promise in enhancing treatment efficacy and mitigating adverse effects associated with standard therapies such as chemotherapy, immunotherapy and hormone therapy (19,92).

Critical evaluation of the literature reveals a growing body of evidence supporting the impact of gut microbiota on PCa. For instance, Liss *et al* (93) identified specific bacterial species associated with PCa, suggesting a role for microbiota in disease pathogenesis. Furthermore, Matsushita *et al* (56) reported that gut microbiota metabolites, particularly SCFAs, promote PCa growth, indicating a potential therapeutic avenue through dietary fiber manipulation. The therapeutic potential of the gut microbiota is further supported by studies showing that probiotics can enhance the response to treatment and reduce postoperative infections, suggesting their utility as an adjuvant therapy (94). FMT has also demonstrated potential in modifying the gut microbiota to improve treatment responses, although the clinical efficacy of such interventions requires further exploration (69).

Despite the promising findings, there is a noted inconsistency in the results across studies, which may be attributed to variations in study design, population demographics and methodology (53). For example, while some studies report an increase in *Bacteroides* and *Streptococcus* in patients with PCa, others find a decrease in *Faecalibacterium prausnitzii*, highlighting the complexity of the gut microbiota's role in PCa (64,65).

Notwithstanding the promising potential of microbiota-targeted therapies, several critical limitations must be acknowledged. The efficacy of probiotics is highly strain-specific and beneficial effects observed with one strain, such as *Lactobacillus rhamnosus* GG (83), cannot be generalized to other strains or probiotic formulations (84). Furthermore, substantial inter-individual variability in baseline gut microbiota composition, driven by factors such as genetics, diet and prior antibiotic exposure (52), markedly influences responses to interventions, complicating the development of universal therapeutic recommendations. Patient heterogeneity also extends to disease status and prior treatments, which may alter the gut ecosystem and modulate intervention outcomes (69). Safety considerations are equally paramount. While probiotics and prebiotics are generally regarded as safe, the long-term consequences of microbiota manipulation, especially in immunocompromised cancer patients, remain inadequately studied. More invasive approaches, such as FMT, carry risks of pathogen transmission, unintended microbial engraftment and unpredictable shifts in microbial communities that could potentially exacerbate inflammation or promote resistance pathways (92,95). Therefore, future clinical applications must incorporate rigorous safety monitoring, strain-level characterization and personalized strategies that account for individual microbiome profiles and clinical contexts.

6. Current limitations and challenges

The gut microbiota has emerged as a significant player in the pathogenesis and progression of PCa, yet several limitations and challenges hinder its clinical application as a therapeutic target (50). One of the primary challenges is the complexity and variability of the gut microbiota across individuals. Factors such as diet, genetics, age and environmental influences contribute to this variability, making it difficult to establish a standardized microbiome profile that correlates with PCa risk or treatment response (14,19). This heterogeneity complicates the interpretation of microbiome studies and the generalization of findings across diverse populations.

The interpretation of gut microbiota studies in PCa is heavily influenced by the diversity of research designs employed, including observational, interventional, cross-sectional and longitudinal approaches. Observational studies, such as case-control and cohort designs, have been instrumental in identifying associations between specific microbial taxa and PCa risk or progression (53,56). However, these studies are prone to confounding factors, including diet, lifestyle and comorbidities, and cannot establish causality. Interventional studies, such as randomized controlled trials (RCTs) investigating probiotics or dietary modifications (55), offer stronger evidence for causal relationships but are often limited by small sample sizes, short durations and heterogeneous intervention protocols. Cross-sectional studies (57) provide a snapshot of microbial composition at a single time point, which is useful for hypothesis generation but cannot capture dynamic changes in the microbiome over time or in response to disease progression or treatment. By contrast, longitudinal studies allow for the assessment of temporal changes and are more suited for evaluating the microbiome's role in disease progression or treatment response (59). Nevertheless, they are resource-intensive and may still be affected by unmeasured confounders. The variability in study designs contributes markedly to the inconsistency of reported findings and complicates the comparison and synthesis of results across studies. Therefore, future research should prioritize well-designed, prospective longitudinal studies and RCTs with standardized methodologies to enhance the reliability and generalizability of conclusions.

Moreover, the methodologies employed in microbiome research often vary markedly, leading to inconsistent results.

For instance, studies utilizing different sampling techniques (for example, stool vs. urine vs. tissue) and analytical methods (for example, 16S rRNA sequencing vs. shotgun metagenomics) can yield divergent microbiome compositions and associations with PCa (53,56). Such discrepancies highlight the need for standardized protocols to ensure comparability and reproducibility of results. Furthermore, the lack of consensus on the definition of 'healthy' compared with 'dysbiotic' microbiomes poses additional challenges in interpreting the implications of microbiome alterations in patients with PCa (96).

Another significant limitation is the current understanding of the mechanisms by which gut microbiota influences PCa. While certain bacterial taxa, such as *Bacteroides massiliensis* and *Akkermansia muciniphila*, have been implicated in PCa progression, the precise pathways and interactions involved remain poorly characterized (14,92). For example, the role of microbial metabolites, such as SCFAs, in modulating inflammation and hormone levels in the prostate is still under investigation, necessitating further research to elucidate these mechanisms (69).

Additionally, the therapeutic potential of modulating the gut microbiota through interventions such as probiotics, prebiotics and FMT faces several obstacles (95). The efficacy of these treatments is often inconsistent, with some studies reporting beneficial effects while others show no significant impact on PCa outcomes (97,98). This inconsistency may stem from variations in individual microbiome composition and the specific strains used in probiotic formulations, underscoring the need for tailored approaches based on individual microbiome profiles. Furthermore, the safety and long-term effects of manipulating the gut microbiota in patients with PCa are not well understood. Concerns regarding the potential for adverse effects, such as the introduction of pathogenic bacteria or the exacerbation of existing conditions, necessitate careful consideration and monitoring in clinical settings (92).

7. Future directions

The exploration of the gut microbiota as a potential modulator of PCa pathogenesis and progression represents an exciting frontier in cancer research. To translate recent associative findings into actionable clinical strategies, future investigations must prioritize several key areas through coordinated and rigorous scientific approaches.

A primary imperative is the establishment of large-scale, multiethnic prospective cohorts. Such studies are essential to account for the profound heterogeneity in gut microbiota composition influenced by genetics, diet, geography and lifestyle (14,29,51). These initiatives should employ standardized methodologies for sample collection, DNA sequencing (preferentially shotgun metagenomics) and bioinformatic analysis to minimize technical variability and enable robust cross-study comparisons. This will help identify consistent microbial signatures for PCa risk stratification across diverse populations and clarify the role of the racial disparities that have been highlighted in preliminary research (80).

Moreover, a deeper mechanistic dissection of the gut-prostate axis is crucial. While microbial metabolites such as SCFAs and their involvement in pathways such as IGF1 signaling and chronic inflammation (such as the NF-κB-IL6-STAT3 axis) have been implicated (68,72,99), the precise cause-and-effect relationships remain incompletely defined. Future work should utilize gnotobiotic animal models, organoids and multi-omics integrations (metagenomics, metabolomics, proteomics) to definitively link specific microbial taxa and their metabolic outputs (such as SCFAs, polyamines and secondary bile acids) to molecular events driving PCa initiation, progression and therapy resistance. The role of bacterial components in modulating intratumoral immune responses represents a particularly promising yet underexplored avenue (52).

The therapeutic potential of microbiota modulation demands rigorous evaluation through well-designed interventional trials. Promising strategies include targeted probiotic and prebiotic formulations, personalized dietary interventions (such as Mediterranean, high-fiber, or polyphenol-rich diets) and FMT (19,69,88,92). Future clinical trials must move beyond observational correlations and focus on randomized controlled designs that assess the efficacy of these interventions in improving responses to standard therapies (such as ADT, immunotherapy and chemotherapy) and mitigating treatment-related adverse effects. A critical aspect will be to develop personalized approaches that consider an individual's baseline microbiome, ensuring that interventions are tailored for maximal efficacy (52,84).

Finally, fostering interdisciplinary collaboration among oncologists, microbiologists, immunologists, nutritionists and bioinformaticians is paramount. Such synergy is necessary to unravel the complex interactions between diet, microbiota and host physiology. The integration of artificial intelligence and machine learning with microbiome data holds significant promise for developing predictive models of disease progression and treatment response (19). By systematically addressing these priorities, including standardized large-scale cohorts, mechanistic elucidation, targeted interventional trials and interdisciplinary collaboration, the field can accelerate the translation of gut microbiota research into novel diagnostic tools and personalized therapeutic strategies for PCa, ultimately improving patient outcomes.

In summary, the gut microbiota represents a promising, yet complex, modulator in PCa pathogenesis. Future research should focus on addressing the existing gaps in understanding microbial diversity, elucidating mechanisms of action and translating insights into clinical applications. By prioritizing these future directions, we enhance our potential to develop innovative strategies that leverage the gut microbiota in the prevention and treatment of PCa, ultimately contributing to improved patient outcomes.

8. Conclusions

The present review highlighted the emerging role of gut microbiota as a potential modulator in PCa pathogenesis and progression, underscoring significant associations between microbial composition and cancer outcomes. While current studies demonstrate the promise of gut microbiota modulation as a novel strategy for PCa prevention and treatment, inconsistencies in methodologies and findings warrant caution. Further investigations are necessary to establish causative relationships and identify actionable therapeutic pathways. Continued

research will be crucial in integrating gut microbiota insights into clinical practice, ultimately enhancing patient management and outcomes in PCa.

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Availability of data and materials

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Authors' contributions

ZH, YX and QZ contributed to the manuscript conception. ZH, KC and RZ were involved in drafting the manuscript and revising it critically for important intellectual content. HS, LL, YL, JH and JW have revised the article for content and language. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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