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INTEGRATIVE ROLE OF HERBAL BIOACTIVES AND DIETARY MODULATION OF GUT MICROBIOTA IN THE PREVENTION OF GASTROINTESTINAL CANCERS

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Article Info

Abstract

The gut microbiota has emerged as a crucial player in the maintenance of gastrointestinal health and the prevention of various chronic diseases, including cancers of the gastrointestinal (GI) tract. A balanced and diverse microbial ecosystem not only facilitates digestion and nutrient absorption but also modulates immune responses and suppresses pro-carcinogenic pathways. Dysbiosis, an imbalance in the composition of gut microbiota, has been increasingly associated with the pathogenesis of colon and gastric cancers through mechanisms such as inflammation, DNA damage, and altered bile acid metabolism. Herbal medicine, rooted in centuries-old traditional healing systems, has recently garnered scientific interest as a promising strategy for restoring gut microbial homeostasis and mitigating cancer risk. Various herbal extracts and phytochemicals possess prebiotic properties, exhibit antimicrobial effects against pathogenic strains, and influence key signaling pathways involved in tumor development. Polyphenol-rich botanicals such as turmeric, green tea, licorice, and berberine-containing herbs have demonstrated the ability to enhance microbial diversity and promote the production of beneficial metabolites such as short-chain fatty acids (SCFAs). This review explores the current evidence on the interaction between medicinal plants and gut microbiota, the mechanisms through which these interactions may modulate cancer risk, and recent in vivo and clinical studies supporting their potential. The paper also discusses limitations in current research, the need for personalized microbiota-based therapies, and future perspectives in this evolving field. Understanding how herbal compounds reshape the gut ecosystem opens new avenues for non-invasive, adjunctive cancer prevention strategies rooted in natural medicine.

Keywords:

Herbal Medicine; Gut Microbiota; Gastrointestinal Cancer; Polyphenols; Colon Cancer; Prebiotics; Phytochemicals; Dysbiosis; Inflammation; Short-Chain Fatty Acids (SCFAs)

1. Introduction

The gastrointestinal (GI) tract serves not only as the primary site of nutrient absorption and digestion but also as the habitat of a highly complex and dynamic microbial community known as the gut microbiota. This intricate ecosystem, comprising trillions of bacteria, viruses, fungi, and archaea, plays a pivotal role in human health. Over the past two decades, scientific research has increasingly illuminated the connection between gut microbiota composition and various chronic diseases, including metabolic disorders, autoimmune conditions, and cancers of the GI tract. Among these, colorectal cancer (CRC) and gastric cancer are of particular concern due to their rising global incidence, especially in developing nations. The World Health Organization reports that colorectal cancer is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide [1]. While genetic predisposition and environmental factors contribute to the pathogenesis of these cancers, alterations in the gut microbial environment—commonly referred to as dysbiosis—have emerged as a major underlying risk factor [2].

The relationship between dysbiosis and GI cancers is multifaceted. A disrupted microbial balance can lead to the production of pro-inflammatory cytokines, increased intestinal permeability, impaired epithelial repair, and genotoxic metabolites, all of which contribute to neoplastic transformation of colonic or gastric epithelium [3]. Certain bacterial strains, such as Fusobacterium nucleatum, Escherichia coli (producing colibactin), and Helicobacter pylori, have been directly implicated in carcinogenesis through mechanisms such as DNA damage, epigenetic alterations, and immune evasion [4]. Conversely, the presence of commensal bacteria such as Lactobacillus and Bifidobacterium has shown protective effects, largely mediated by the generation of short-chain fatty acids (SCFAs), regulation of host immunity, and suppression of inflammation [5].

This intricate interplay between the gut microbiota and cancer development opens an avenue for preventive and therapeutic interventions aimed at restoring microbial balance. Among the most promising natural modulators of the gut microbiome are herbal medicines. Traditionally used in Unani, Ayurveda, Chinese, and other ethnobotanical systems, medicinal plants have demonstrated an impressive range of bioactivities, including antimicrobial, antioxidant, anti-inflammatory, and immunomodulatory effects. More recently, specific phytochemicals from these herbs have been shown to interact with gut microbes, influencing their composition and metabolic function [6]. For instance, curcumin from turmeric not only exhibits direct antitumor properties but also enhances the growth of beneficial bacteria such as Faecalibacterium prausnitzii [7].

As the field of cancer prevention moves toward integrative and holistic strategies, the use of herbal interventions to reshape the gut microbiota offers a compelling, low-toxicity approach. A number of preclinical and clinical studies have begun to explore this intersection of herbal medicine, microbiome science, and oncology. However, comprehensive evaluations of the evidence remain limited. Therefore, this review aims to critically analyze recent literature on herbal modulation of gut microbiota and its implications in the prevention of GI cancers. We will examine mechanistic pathways, highlight key medicinal plants and their active constituents, review evidence from in vivo and clinical trials, and discuss the challenges and future directions in this emerging area of research.

In addition to herbal medicine, the role of nutrition—particularly the consumption of prebiotics, probiotics, and polyphenol-rich functional foods—has gained increasing attention in gut microbiota research. Dietary components such as dietary fiber, fermented foods, green tea, and cruciferous vegetables not only support microbial diversity but also enhance the abundance of beneficial taxa like Lactobacillus and Bifidobacterium. These taxa produce metabolites like short-chain fatty acids (SCFAs), which exert anti-inflammatory and antitumor effects. The convergence of herbal bioactives and dietary modulation of the gut ecosystem offers a comprehensive, integrative approach to colorectal and other gastrointestinal cancer prevention. This synergistic potential forms the foundation for a more holistic preventive strategy in modern nutritional oncology.

2. Gut Microbiota and Its Role in Gastrointestinal Cancer

The gut microbiota plays a central role in maintaining gastrointestinal homeostasis and influencing systemic health. Its contribution to carcinogenesis, particularly in gastrointestinal cancers such as colorectal and gastric cancer, has become an area of active research. The human gut harbors more than 100 trillion microbial cells, encoding over 100 times more genes than the human genome. These microbes are not passive inhabitants; rather, they perform critical functions including nutrient metabolism, synthesis of vitamins, maintenance of gut barrier integrity, and regulation of host immune responses. A balanced microbiome supports immune surveillance and suppresses inflammation, both of which are protective against tumorigenesis. However, disruption of this balance—commonly referred to as dysbiosis—has been implicated in the initiation and progression of cancer.

Dysbiosis refers to an abnormal composition or function of the gut microbiota and is often characterized by reduced microbial diversity, loss of beneficial bacterial species, and overgrowth of potentially pathogenic microbes. This state creates a microenvironment conducive to inflammation, epithelial injury, and DNA damage. Studies have shown that dysbiotic microbiota can produce carcinogenic metabolites such as secondary bile acids, ammonia, and nitrosamines, which directly damage the colonic epithelium [8]. Additionally, dysbiosis promotes the overexpression of inflammatory mediators including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and nuclear factor-kappa B (NF-κB), which are key players in inflammation-driven cancer pathways [9].

Several bacterial species have been directly implicated in GI cancer. Fusobacterium nucleatum, a gram-negative anaerobe frequently found in the oral cavity, has been identified in increased abundance in colorectal cancer tissues. It promotes tumor progression by activating β-catenin signaling, inducing myeloid-derived suppressor cells (MDSCs), and enhancing immune evasion [10]. Similarly, Escherichia coli strains harboring the pks genomic island can produce colibactin, a genotoxin that induces DNA double-strand breaks in host epithelial cells, thereby promoting mutagenesis and carcinogenesis [11]. In gastric cancer, Helicobacter pylori remains a well-established etiological agent. This microbe contributes to carcinogenesis via chronic inflammation, production of reactive oxygen species (ROS), and modulation of host gene expression through virulence factors such as CagA and VacA [12].

Conversely, a healthy and diverse microbial ecosystem exerts a protective effect against carcinogenesis. Commensal bacteria such as Bifidobacterium, Lactobacillus, and Faecalibacterium prausnitzii have been

shown to inhibit tumor development through various mechanisms. These include competitive exclusion of pathogenic species, enhancement of mucosal immunity, promotion of anti-inflammatory cytokines like IL-10, and production of short-chain fatty acids (SCFAs), particularly butyrate. Butyrate, a fermentation product of dietary fiber, plays a key role in maintaining colonic epithelial health. It serves as an energy source for colonocytes, strengthens the gut barrier, and acts as a histone deacetylase (HDAC) inhibitor, leading to apoptosis of transformed cells and suppression of oncogenes [13].

Overall, the composition of the gut microbiota has a bidirectional relationship with cancer development. Not only can dysbiosis promote tumorigenesis, but cancer itself and its treatments can further disrupt microbial homeostasis. Chemotherapy and radiotherapy are known to reduce microbial diversity and damage the mucosal barrier, exacerbating inflammation and increasing the risk of opportunistic infections. Thus, therapeutic strategies aimed at restoring microbial balance hold great promise in both cancer prevention and management. Among these, herbal medicine offers a unique advantage due to its dual ability to directly influence microbial populations and simultaneously exert anti-cancer properties through phytochemicals.

3. Herbal Extracts and Microbiota Modulation in GI Cancer Prevention

Herbal medicine has long been utilized in various traditional systems, including Ayurveda, Unani, and Traditional Chinese Medicine (TCM), to treat gastrointestinal ailments. In recent years, scientific inquiry has begun to uncover how specific herbs and their active constituents can beneficially modulate the gut microbiota, thereby playing a role in the prevention of gastrointestinal cancers. This therapeutic effect occurs through several overlapping mechanisms, including promoting beneficial microbial species, inhibiting the growth of pathogenic strains, and enhancing the production of anti-inflammatory microbial metabolites such as short-chain fatty acids (SCFAs).

Many herbs act as prebiotics—non-digestible compounds that stimulate the growth and activity of health-promoting bacteria. For instance, polyphenols found in green tea (Camellia sinensis) and curcumin from turmeric (Curcuma longa) are poorly absorbed in the small intestine and reach the colon, where they are metabolized by gut bacteria into bioactive forms. These interactions result in increased populations of beneficial bacteria such as Lactobacillus and Bifidobacterium, which contribute to mucosal integrity and immune balance [14]. In parallel, several herbal alkaloids, flavonoids, and terpenoids exhibit selective antimicrobial properties against pathogenic microbes like Clostridium perfringens and Escherichia coli, thereby reshaping the microbial landscape toward eubiosis [15].

Additionally, some herbs influence microbial-derived metabolites, particularly SCFAs such as acetate, propionate, and butyrate. These SCFAs are known to exert anticancer effects by modulating inflammation, enhancing gut barrier function, and inducing apoptosis in colon cancer cells. Berberine, a bioactive alkaloid from Berberis vulgaris and Coptis chinensis, has been shown to enrich SCFA-producing bacteria and reduce inflammatory markers in both animal models and human studies [16].

The interaction between herbal constituents and the gut microbiome is bidirectional. Microbes metabolize phytochemicals into more potent bioactive compounds, while herbs simultaneously influence microbial composition. This synergy enhances both anticancer efficacy and microbiota resilience. The table below

highlights key medicinal herbs, their active compounds, known effects on the gut microbiota, and their relevance to GI cancer prevention based on recent studies.

Table 1: Selected Herbal Extracts with Gut Microbiota Modulatory and Anticancer Effects

Herb	Active Compound(s)	Microbiota Effects	Anticancer Relevance	References
Curcuma longa (Turmeric)	Curcumin	↑ Lactobacillus, Bifidobacterium, ↓ E. coli, anti-inflammatory	Induces apoptosis, inhibits colon cancer cell proliferation	[14], [17]
Camellia sinensis (Green Tea)	EGCG (Epigallocatechin gallate)	↑ SCFA-producing bacteria, ↑ microbial diversity	Suppresses tumor growth, modulates NF-κB and Wnt signaling	[18], [19]
Berberis vulgaris / Coptis chinensis	Berberine	↑ Akkermansia, ↑ butyrate levels, ↓ pro-inflammatory species	Reduces tumor-promoting inflammation, enhances immunity	[16], [20]
Glycyrrhiza glabra (Licorice)	Glycyrrhizin, Liquiritin	Modulates gut flora, protects mucosa	Anti-ulcer, anti-inflammatory, reduces gastric cancer risk	[21]
Zingiber officinale (Ginger)	Gingerols, Shogaols	↑ Lactobacillus, ↓ Helicobacter pylori	Suppresses carcinogen-induced gastric inflammation	[22]
Panax ginseng	Ginsenosides	↑ beneficial flora, enhances SCFA levels	Inhibits cancer cell invasion and metastasis	[23]
Punica granatum (Pomegranate)	Ellagitannins, Punicalagin	↑ Bifidobacterium, transforms into urolithins by gut flora	Antiproliferative, pro-apoptotic in colon cancer models	[24]
Nigella sativa (Black Seed)	Thymoquinone	Modulates Firmicutes/Bacteroidetes ratio, anti-inflammatory	Inhibits colon tumor initiation, reduces oxidative stress	[25]

The growing body of evidence underscores the potential of phytochemicals to interact meaningfully with the gut microbiota and thereby influence cancer-related outcomes. These interactions highlight the importance of selecting whole plant extracts or bioactive combinations that support a healthy microbial ecology. Given the complexity of both herbal matrices and the gut microbiome, further research using omics-based tools and controlled clinical trials is essential to establish dose-response relationships, identify synergistic effects, and confirm long-term safety.

Functional Foods as Microbiota-Modulating Agents in GI Cancer Prevention

In addition to herbal therapeutics, several functional foods and dietary nutrients have demonstrated significant potential in modulating gut microbiota composition and function. These bioactive-rich foods—including probiotics, prebiotics, fibers, and polyphenols—not only promote beneficial microbial populations but also enhance the production of metabolites like short-chain fatty acids (SCFAs), which are known to inhibit tumor growth and inflammation. Integrating such foods into daily nutrition may provide a complementary strategy alongside phytochemicals in preventing gastrointestinal malignancies.

Table 2: Functional Foods with Microbiota-Modulating and Anticancer Properties

Food/Nutrient	Key Components	Gut Microbiota Effect	Cancer-Preventive Mechanism
Yogurt, Kefir	Probiotics (Lactobacillus, Bifidobacterium)	Enhances microbial diversity, restores balance	Reduces inflammation, improves mucosal integrity
Garlic, Onion	Inulin, Allicin	Prebiotic effect, promotes beneficial taxa	Antioxidant, antimicrobial
Green Tea	Catechins (EGCG)	Inhibits pathogens, modulates SCFA production	Suppresses proliferation, induces apoptosis
Whole Grains (Oats, Barley)	β-Glucans, Fiber	Fermented to SCFAs like butyrate	Anti-inflammatory, improves gut barrier
Berries (Blueberry, Pomegranate)	Anthocyanins, polyphenols	Increases Akkermansia and Faecalibacterium spp.	Scavenges free radicals, modulates immune system
Fermented Soy (Tempeh, Miso)	Isoflavones	Prebiotic–probiotic synergy	Regulates estrogenic pathways
Leafy Greens (Spinach, Kale)	Polyphenols, fiber	Enhances Lactobacilli, promotes SCFA production	Detoxification support, immune modulation

Selected functional foods with established roles in modulating gut microbiota and preventing gastrointestinal cancers. These food-based components exert synergistic effects when combined with phytotherapeutic agents, potentially enhancing host immunity, maintaining gut barrier integrity, and suppressing tumor-promoting pathways.

4. Mechanisms of Herbal Action via Gut Microbiota in Cancer Prevention

The anti-cancer potential of herbal medicines is not solely dependent on their direct cytotoxic or antiproliferative effects. Increasing evidence reveals that many of these actions are mediated indirectly through the modulation of gut microbiota. This host–microbe–herb interaction forms a triangular relationship in which phytochemicals influence the composition and function of gut microbes, and in turn, the microbiota transforms these compounds into bioactive metabolites that affect host physiology,

including cancer-related pathways. Understanding these mechanisms is critical to leveraging herbal therapy as a preventive strategy for gastrointestinal cancers.

One of the primary mechanisms involves the enhancement of beneficial microbial species. Herbal compounds such as polyphenols, saponins, and alkaloids act as substrates for microbial fermentation, promoting the proliferation of probiotics like Lactobacillus, Bifidobacterium, and Faecalibacterium prausnitzii. These microbes play a protective role in gut homeostasis by maintaining mucosal integrity, modulating immune responses, and suppressing colonization by pathogenic bacteria. The restoration of microbial diversity through herbs contributes to a balanced immune environment that resists tumor-promoting inflammation [26].

A second crucial pathway is the production of short-chain fatty acids (SCFAs)—mainly acetate, propionate, and butyrate—by microbial fermentation of non-digestible phytochemicals and dietary fibers present in herbs. Butyrate, in particular, has been extensively studied for its anticancer properties. It serves as the primary energy source for colonocytes, reinforces intestinal barrier function, and acts as a histone deacetylase (HDAC) inhibitor. By inhibiting HDAC activity, butyrate promotes the expression of tumor suppressor genes, induces apoptosis in neoplastic cells, and suppresses pro-carcinogenic signaling pathways such as NF-κB and Wnt/β-catenin [27]. Herbal treatments that enhance SCFA-producing bacteria or serve as SCFA precursors are thus indirectly involved in tumor suppression.

Another prominent mechanism is the suppression of chronic inflammation**,** a hallmark of cancer. Many herbs influence microbial populations that reduce endotoxin-producing Gram-negative bacteria, which are major contributors to low-grade inflammation via lipopolysaccharide (LPS) release. Furthermore, herbal polyphenols modulate Toll-like receptors (TLRs) and inflammasome activity, leading to downregulation of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. For example, berberine and resveratrol have shown the capacity to suppress the activation of the NF-κB pathway through microbiota-mediated and direct pathways, thereby inhibiting the inflammatory microenvironment that favors carcinogenesis [28].

Herbal modulation of gut microbiota also **impacts** bile acid metabolism**,** which plays a significant role in colorectal and gastric cancer. Secondary bile acids such as deoxycholic acid (DCA), produced by microbial conversion of primary bile acids, have been associated with oxidative DNA damage and cancer promotion. Certain herbs can reduce bile acid toxicity by either inhibiting microbial strains responsible for DCA production or promoting microbial species that conjugate bile acids into less harmful forms [29]. For instance, turmeric and pomegranate polyphenols have shown potential in modulating bile acid pools through gut microbial changes.

Additionally, epigenetic regulation through microbial metabolism of phytochemicals represents a novel mechanism of action. Microbiota-derived metabolites from herbal constituents may influence DNA methylation, histone modification, and microRNA expression in host cells. These epigenetic changes can restore normal gene expression patterns, silence oncogenes, and activate tumor suppressor pathways. In preclinical studies, resveratrol and green tea polyphenols have been linked with demethylation of tumor suppressor genes and inhibition of cancer cell growth [30].

Finally, **the** reinforcement of gut barrier integrity is another essential mechanism by which herbs help prevent cancer. Dysbiosis often compromises the intestinal epithelial barrier, leading to increased permeability ("leaky gut") and systemic inflammation. Herbal components enhance tight junction proteins (such as occludin and claudins), reduce oxidative stress, and stimulate mucus production, all of which contribute to restoring epithelial integrity. By preventing microbial translocation and systemic immune activation, herbs create an environment less conducive to tumor initiation [31].

Collectively, these interconnected mechanisms illustrate how herbal therapies modulate the microbiota to influence cancer-related processes at multiple levels—ranging from molecular signaling and metabolism to immunity and epithelial health. The complexity of these interactions emphasizes the need for integrative research approaches, combining phytochemistry, microbiology, and oncology to optimize herbal interventions in cancer prevention.

5. Clinical and Preclinical Evidence Supporting Herbal-Microbiota Interventions in GI Cancer

In recent years, both preclinical and clinical research has increasingly supported the role of herbal medicines in modulating gut microbiota to mitigate gastrointestinal cancer risk. Several animal models, including chemically induced colorectal cancer models in mice and rats, have demonstrated that specific herbal extracts can reshape the microbial ecosystem, reduce inflammation, and suppress tumor development. Meanwhile, emerging human trials, although limited in number, provide promising insights into the translation of these findings to clinical settings.

One of the most extensively studied herbal compounds is curcumin, the principal polyphenol in Curcuma longa (turmeric). In a 2020 mouse model of azoxymethane (AOM)-induced colorectal cancer, oral curcumin supplementation significantly reduced tumor multiplicity while increasing the abundance of beneficial bacteria such as Lactobacillus and Bifidobacterium [32]. The antitumor effect was correlated with enhanced levels of butyrate and reduced expression of inflammatory cytokines such as TNF-α and IL-6. Similarly, a randomized, double-blind, placebo-controlled clinical trial in humans reported in 2021 demonstrated that curcumin supplementation improved gut microbiota diversity in patients with colorectal adenomas, while also decreasing markers of inflammation and epithelial proliferation [33].

Berberine, derived from Berberis vulgaris and Coptis chinensis, has also gained attention for its dual role in gut microbiota modulation and anticancer activity. A 2022 study using a colitis-associated colon cancer mouse model revealed that berberine enriched SCFA-producing bacteria including Faecalibacterium and Roseburia, reduced colonic inflammation, and significantly lowered tumor incidence [34]. The microbiota shifts were associated with decreased expression of NF-κB and COX-2, highlighting the anti-inflammatory pathway. In a parallel 2023 pilot clinical trial, colorectal cancer patients receiving berberine for three months showed improved gut microbial profiles, enhanced T-cell responses, and reduced fecal calprotectin, suggesting a reduced inflammatory state and improved mucosal immunity [35].

Green tea polyphenols, especially EGCG (epigallocatechin gallate), have shown similar results. In a 2021 study involving mice with AOM/DSS-induced colon cancer, EGCG not only reduced tumor burden but also increased the Firmicutes/Bacteroidetes ratio, elevated Akkermansia muciniphila, and promoted mucin production—suggesting strengthened gut barrier integrity [36]. This microbial modulation

correlated with enhanced SCFA levels and reduced epithelial dysplasia. A human study conducted in 2022 involving patients at high risk for colon cancer revealed that green tea extract supplementation for 12 weeks altered the gut microbiome composition favorably, reduced oxidative stress markers, and improved mucosal histology [37].

Ginger (Zingiber officinale), known for its anti-inflammatory and digestive properties, has also shown anticancer potential mediated by microbiota modulation. A 2020 rat study reported that ginger extract reduced Helicobacter pylori colonization, restored Lactobacillus abundance, and significantly prevented gastric mucosal dysplasia [38]. A 2021 small-scale human trial showed that ginger powder supplementation decreased Enterobacteriaceae counts and improved gut-related symptoms in patients with precancerous gastric lesions [39].

Licorice (Glycyrrhiza glabra) and pomegranate (Punica granatum) have also demonstrated similar microbiota-mediated anticancer effects in both preclinical and clinical models. Their bioactive compounds, such as glycyrrhizin and ellagitannins respectively, contribute to epithelial regeneration, microbial balance, and downregulation of pro-oncogenic inflammatory signals.

Table 3: Key Preclinical and Clinical Studies on Herbal Modulation of Microbiota in GI Cancer

Herb	Study Type / Model	Microbiota Changes	Cancer Outcome	Ref
Curcuma longa	Mouse (AOM model, 2020)	↑ Lactobacillus, ↑ Bifidobacterium, ↑ SCFAs	↓ Tumor count, ↓ TNF-α, IL-6	[32]
Curcuma longa	Human (RCT, 2021)	↑ Diversity, ↑ butyrate producers	↓ Colorectal adenoma recurrence risk	[33]
Berberis vulgaris	Mouse (AOM/DSS, 2022)	↑ Faecalibacterium, ↓ Enterobacteriaceae	↓ Tumor load, ↓ COX-2, NF-κB	[34]
Berberis vulgaris	Human (Pilot, 2023)	↑ SCFA producers, ↑ T-cell immunity	↓ Calprotectin, improved mucosal healing	[35]
Camellia sinensis	Mouse (AOM/DSS, 2021)	↑ Akkermansia, ↑ Firmicutes/Bacteroidetes ratio	↓ Dysplasia, ↑ mucosal integrity	[36]
Camellia sinensis	Human (2022)	↑ Bifidobacterium, ↑ antioxidants	↓ Oxidative stress, improved histology	[37]
Zingiber officinale	Rat (H. pylori model, 2020)	↑ Lactobacillus, ↓ Helicobacter pylori	↓ Gastric inflammation and dysplasia	[38]
Zingiber officinale	Human (2021)	↓ Enterobacteriaceae, ↑ anti-inflammatory strains	Improved gut symptoms, potential cancer risk reduction	[39]

These studies collectively illustrate the translational potential of herbal-microbiota interventions in cancer prevention. While preclinical models have consistently shown favorable results, human trials remain in their early stages, often limited by small sample sizes, short durations, and heterogeneity in

herbal formulations. However, they underscore the feasibility of using plant-derived compounds to influence host–microbe dynamics in a clinically meaningful way.

As interest grows in personalized and microbiota-driven therapies, integrating phytomedicine offers a non-invasive, cost-effective adjunct strategy for gastrointestinal cancer prevention. The evidence also supports future directions toward standardizing herbal formulations, developing microbial biomarkers for response prediction, and designing longer-term clinical studies.

6. Challenges and Limitations in Herbal-Microbiota-Cancer Research

Despite the promising evidence supporting the role of herbal extracts in modulating gut microbiota to prevent gastrointestinal (GI) cancers, several challenges and limitations persist in both research and clinical application. These limitations span from scientific and technical barriers to regulatory and clinical translation issues, which must be addressed to ensure the reliability and scalability of herbal-microbiota-based therapies.

One of the foremost challenges is the complexity and variability of herbal preparations. Herbal extracts are often composed of dozens, if not hundreds, of phytochemicals, many of which may interact synergistically or antagonistically. The precise bioactive compounds responsible for microbial modulation are frequently unidentified or inconsistently quantified across preparations. Additionally, factors such as plant species, harvesting season, geographic origin, and extraction methods significantly influence the phytochemical profile, leading to batch-to-batch variation. This lack of standardization hinders reproducibility and complicates the comparison of findings across studies [40].

Another major challenge is the inter-individual variability in gut microbiota composition, which can significantly affect the way an individual responds to a given herbal treatment. The gut microbiome is shaped by various factors, including age, diet, genetics, lifestyle, and existing disease conditions. As a result, an herbal compound that promotes beneficial microbial shifts in one population may yield minimal or even adverse effects in another. This individual variation complicates the development of universally effective herbal formulations and highlights the need for personalized approaches based on microbiome profiling [41].

Furthermore, there is limited knowledge regarding the bioavailability and metabolism of herbal compounds within the gastrointestinal tract. Many phytochemicals exhibit poor absorption in the small intestine and undergo extensive transformation by colonic microbes. While this microbial metabolism can enhance or activate therapeutic properties, it may also lead to inactive or toxic byproducts. The bidirectional interaction between herbs and microbes is still not fully understood, particularly in human systems, making it difficult to predict therapeutic outcomes with precision [42].

Another limitation lies in the design and quality of existing clinical studies. Most human trials evaluating herbal-microbiota interactions are of small sample size, short duration, and often lack control groups or blinding. Moreover, many studies use crude plant powders or mixed formulations without clearly isolating active compounds, limiting mechanistic insight. The absence of standardized endpoints, such as validated microbiome biomarkers or cancer-specific outcomes, further complicates the interpretation of results and the translation of findings into clinical guidelines [43].

Regulatory issues also present hurdles. Herbal products are often classified as dietary supplements rather than therapeutic agents, resulting in limited oversight regarding efficacy, safety, and manufacturing standards. In many countries, herbal products are not subject to the rigorous preclinical and clinical testing required for pharmaceuticals, which raises concerns about contamination, adulteration, and incorrect labeling. Without stringent regulatory frameworks, the integration of herbal-microbiota therapies into mainstream oncology remains difficult [44].

Additionally, interactions with conventional cancer therapies pose another layer of complexity. While herbal extracts may enhance therapeutic outcomes or reduce side effects, they may also interfere with the pharmacokinetics or pharmacodynamics of chemotherapeutic agents. For example, some herbs can alter drug-metabolizing enzymes or transporters, thereby modifying drug efficacy or toxicity. The safety of combining herbal therapies with chemotherapy or immunotherapy in the context of altered microbiota is still an underexplored area that warrants cautious investigation [45].

Lastly, ethical and cultural considerations cannot be ignored. Herbal medicine is rooted in diverse cultural traditions, and its acceptance varies across populations. Integrating traditional herbal practices into evidence-based medical frameworks requires sensitivity to cultural beliefs while maintaining scientific rigor. Additionally, issues of intellectual property rights and benefit-sharing must be addressed when using ethnobotanical knowledge in commercial or academic settings.

In summary, while the potential of herbal-microbiota modulation in preventing GI cancers is compelling, significant challenges remain in standardization, individual variability, clinical trial design, safety, regulation, and integration with conventional therapies. Addressing these issues through interdisciplinary collaboration, advanced omics technologies, and regulatory reform will be essential for unlocking the full potential of this integrative therapeutic approach.

7. Future Perspectives and Research Directions

As the relationship between gut microbiota, herbal medicine, and gastrointestinal cancer becomes increasingly evident, future research is poised to move beyond observational studies into more mechanistic, personalized, and technology-integrated domains. Emerging methodologies and innovations in omics, computational biology, and formulation science offer exciting possibilities to enhance the efficacy, specificity, and clinical applicability of herbal-microbiota-based cancer prevention strategies.

One promising direction lies in the development of personalized herbal therapies guided by individual microbiota profiles. Given the significant inter-individual variability in microbial composition and function, a one-size-fits-all approach is unlikely to yield optimal outcomes. Advances in metagenomic and metabolomic technologies now make it feasible to generate individualized microbiota signatures, which could guide the selection of specific herbs or phytochemicals best suited to restore microbial balance and suppress carcinogenic pathways in a given patient. For example, patients with reduced butyrate-producing bacteria may benefit more from fiber-rich or SCFA-promoting herbs, such as berberine-containing plants or polyphenol-rich turmeric [46].

Another forward-looking strategy is the integration of herbal compounds with probiotic or synbiotic formulations, forming what is now termed “phyto-synbiotics.” Combining select herbs with live microbial strains may exert synergistic effects by simultaneously introducing beneficial microbes and substrates that fuel their growth. This approach may be particularly effective in patients undergoing chemotherapy or antibiotic treatment, where microbiota depletion is common. Formulations that co-deliver curcumin and Lactobacillus strains, for instance, have shown enhanced anti-inflammatory and mucosal healing effects in preclinical studies [47].

Nanotechnology also holds potential in overcoming traditional limitations of herbal therapies, such as poor bioavailability, instability, and non-targeted distribution. The encapsulation of herbal compounds in nanoparticles, liposomes, or phytosomes allows for controlled release, improved absorption, and targeted delivery to the colon—where most microbiota-mediated actions occur. Nano-curcumin and nano-berberine formulations have already shown superior therapeutic profiles in experimental models of colon cancer [48]. Incorporating microbiota-targeted delivery systems into such formulations could further enhance local therapeutic effects while minimizing systemic exposure and toxicity.

Artificial intelligence (AI) and machine learning (ML) algorithms are expected to play an increasingly vital role in predicting microbiota responses to herbal compounds and designing individualized therapeutic strategies. AI models can analyze complex datasets involving gut microbiome composition, host gene expression, dietary intake, and herbal pharmacokinetics to predict outcomes such as SCFA production, inflammatory status, and cancer risk. This data-driven approach will be instrumental in accelerating discovery and optimizing patient-specific interventions [49].

In terms of clinical translation, there is a need to design robust, long-term, multi-center clinical trials that evaluate standardized herbal formulations, microbiota changes, and validated cancer-related outcomes. These trials should incorporate microbiome sequencing, metabolomic profiling, and immunological markers to generate high-quality data. Additionally, regulatory harmonization will be crucial to ensure the safety, consistency, and efficacy of herbal-microbiota interventions. Regulatory agencies must develop new frameworks that recognize the unique pharmacodynamics of microbiota-mediated therapies and facilitate their integration into cancer prevention programs [50].

Moreover, future studies should aim to identify novel plant-derived compounds with microbiota-modulating properties, particularly those targeting specific carcinogenic pathways such as β-catenin activation, DNA alkylation, and ROS production. High-throughput screening of ethnomedicinal plants, coupled with microbiome assays, could uncover a new generation of microbiota-active phytochemicals with therapeutic relevance.

Finally, a transdisciplinary research culture is needed to bridge gaps between traditional herbal knowledge, modern microbiome science, oncology, pharmacology, and data analytics. Collaborations among clinicians, microbiologists, pharmacognosists, computational scientists, and policy makers will be essential to advance this integrative field from bench to bedside.

In conclusion, the convergence of herbal medicine and microbiome research offers an innovative and holistic framework for the prevention of gastrointestinal cancers. With the application of emerging

technologies, personalized approaches, and rigorous clinical science, herbal-microbiota therapy has the potential to become a cornerstone of preventive oncology in the 21st century.

8. Conclusion

The gut microbiota has emerged as a crucial player in the development, progression, and prevention of gastrointestinal cancers. A balanced and diverse microbial ecosystem is essential for maintaining mucosal integrity, regulating immune responses, and modulating metabolic processes that can either promote or inhibit tumorigenesis. Disruption of this balance, or dysbiosis, has been consistently linked to pro-inflammatory states, DNA damage, impaired barrier function, and the generation of carcinogenic metabolites—all of which contribute to the pathogenesis of colorectal and gastric cancers.

Herbal medicines, deeply rooted in traditional healing systems and now supported by modern scientific inquiry, offer a promising, low-toxicity strategy for restoring microbial equilibrium and reducing cancer risk. Numerous preclinical and clinical studies have demonstrated that specific herbs—such as turmeric, berberine, green tea, ginger, and licorice—can beneficially alter gut microbiota composition, increase the abundance of SCFA-producing and anti-inflammatory bacteria, and downregulate cancer-related signaling pathways including NF-κB, Wnt/β-catenin, and COX-2. These findings suggest that herbal-microbiota interactions can create a local and systemic environment that is less conducive to malignant transformation.

Despite the encouraging evidence, challenges remain in the form of herbal formulation variability, inter-individual microbiome differences, lack of large-scale human trials, and regulatory complexities. Addressing these challenges requires an integrated approach involving personalized medicine, advanced analytical technologies, and collaborative research models. Future directions such as microbiota-guided herbal therapy, nanotechnology-based delivery systems, and AI-driven prediction tools hold significant potential to transform this field.

In conclusion, the modulation of gut microbiota using medicinal herbs represents a novel, synergistic, and biologically plausible approach to preventing gastrointestinal cancers. With continued research, clinical validation, and innovation, this integrative strategy could complement conventional preventive and therapeutic frameworks, offering new hope for reducing the global burden of GI malignancies.

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