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# Gut Microbiota-Derived Natural Metabolites in Obesity-Associated Colorectal Cancer: A Therapeutic Perspective

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## ABSTRACT

The rising global prevalence of obesity has significantly increased the burden of colorectal cancer (CRC), now recognized as one of the leading causes of cancer-related morbidity and mortality worldwide. Recent advances in microbiome research have highlighted the intricate interplay between obesity, gut microbiota, and colorectal carcinogenesis. Obesity-induced dysbiosis not only perturbs intestinal homeostasis but also alters the production of gut microbiota-derived natural metabolites, many of which possess critical bioactive properties. These microbial metabolites such as short-chain fatty acids (SCFAs), secondary bile acids, indole derivatives, and polyphenol catabolites, play pivotal roles in modulating host immunity, inflammation, cell proliferation, and apoptosis. While certain metabolites may exacerbate tumorigenesis, others demonstrate protective or chemopreventive effects, thereby representing a novel frontier for therapeutic exploration. This review provides an integrated overview of how obesity reshapes gut microbial ecology and the metabolic landscape, examines the roles of specific microbial-derived metabolites in colorectal cancer development, and evaluates current and emerging therapeutic strategies that harness these metabolites for cancer prevention and treatment. Understanding the mechanistic underpinnings of these host-microbe interactions offers promising opportunities for precision medicine, including microbiota-targeted dietary interventions, probiotic formulations, and metabolite-based drug development to mitigate the dual burden of obesity and colorectal cancer.
**Keywords**: Gut microbiota, Obesity, Colorectal cancer, Microbial metabolites, Therapeutic strategies

## INTRODUCTION

Colorectal cancer (CRC) represents a significant global health burden, ranking among the top three most commonly diagnosed cancers and a leading cause of cancer-related mortality worldwide[1, 2]. A myriad of genetic, environmental, and lifestyle factors contribute to CRC development, with obesity emerging as one of the most prominent and modifiable risk factors[3, 4]. The global prevalence of obesity has escalated in recent decades, coinciding with a parallel rise in CRC incidence, particularly in younger populations[4]. Obesity-induced carcinogenesis is a multifactorial process involving chronic low-grade inflammation, insulin resistance, dyslipidemia, adipokine imbalance, and, importantly, metabolic reprogramming of host tissues[5–7]. These metabolic alterations not only foster a microenvironment conducive to tumor initiation and progression but also interact with gut-resident microbial populations to modulate cancer risk.

The gut microbiota, a complex and dynamic community of trillions of microorganisms including bacteria, archaea, fungi, and viruses, plays a pivotal role in maintaining host metabolic homeostasis, immune regulation, and gastrointestinal health. Recent advances in high-throughput sequencing and metabolomics have deepened our understanding of the intricate relationship between the gut microbiome and host physiology[8–10]. In the context of obesity and CRC, gut microbial dysbiosis, characterized by a reduction in microbial diversity, a decline in beneficial bacteria, and an overrepresentation of pathogenic species has been consistently observed[11, 12]. This dysbiotic state contributes to the disruption of intestinal barrier integrity, systemic inflammation, altered bile acid metabolism, and the generation of carcinogenic compounds, thereby promoting colorectal tumorigenesis.

Among the most compelling avenues through which the gut microbiota impacts CRC development is the production of natural bioactive metabolites[10, 12, 13]. These small-molecule compounds, derived from microbial fermentation of dietary fibers, amino acids, bile acids, and other host- or microbe-derived substrates, act as crucial signaling molecules that influence host cellular pathways. Metabolites such as short-chain fatty acids (SCFAs), secondary bile acids, tryptophan derivatives, polyamines, and microbial-derived vitamins exert diverse effects on epithelial cell proliferation, immune modulation, apoptosis, angiogenesis, and epigenetic modifications[10, 14]. While some of these metabolites, notably butyrate and other SCFAs, are known for their protective effects against inflammation and cancer, others like deoxycholic acid (a secondary bile acid) have been implicated in promoting DNA damage and oncogenic signaling.



Obesity significantly alters the composition and metabolic function of the gut microbiota, leading to shifts in the production profiles of these key metabolites[15, 16]. For example, obese individuals often exhibit reduced levels of SCFA-producing bacteria such as *Faecalibacterium prausnitzii* and *Roseburia spp.*, which correlates with decreased butyrate levels and a weakened anti-inflammatory gut environment[17]. Conversely, there is often an enrichment of bile-tolerant, pro-inflammatory species such as *Bilophila wadsworthia* and *Bacteroides spp.*, which contribute to the increased production of tumor-promoting metabolites[17]. These obesity-induced changes in microbial ecology and function not only exacerbate intestinal inflammation and metabolic stress but also create a tumor-permissive environment conducive to CRC development[17].

Moreover, the bidirectional relationship between host metabolism and the gut microbiota suggests a synergistic interaction in the context of obesity and CRC[13]. Host metabolic cues, such as elevated insulin and glucose levels, can influence microbial composition and behavior, while microbial metabolites can in turn affect host gene expression, immune responses, and metabolic pathways[18]. This dynamic crosstalk underscores the importance of considering both host and microbial factors in understanding CRC pathogenesis[18].

Given the pivotal role of microbial metabolites in mediating the obesity-CRC axis, they have garnered significant interest as potential therapeutic targets and biomarkers. Modulating the gut microbiota through dietary interventions, prebiotics, probiotics, postbiotics, or even fecal microbiota transplantation (FMT) offers promising strategies for restoring microbial balance and favorably altering metabolite profiles[19]. Additionally, harnessing the beneficial effects of specific metabolites, such as butyrate, indolepropionic acid, or urolithins, may provide novel avenues for chemoprevention and adjuvant therapy in CRC[19]. This review aims to provide a comprehensive overview of the mechanistic interplay between obesity-induced gut microbial dysbiosis, natural microbial metabolite production, and colorectal cancer pathogenesis. It highlights major classes of microbial-derived metabolites, elucidates their functional roles in modulating tumorigenic processes, and explores their therapeutic potential in CRC prevention and treatment. By unraveling the complex metabolic dialogue between the gut microbiota and the host, this review seeks to shed light on novel, microbiota-targeted approaches to mitigate the rising burden of obesity-associated colorectal cancer.

## 2. Obesity, Gut Microbiota, and Colorectal Carcinogenesis

Obesity is a multifactorial condition that significantly reshapes the gut microbial ecosystem and contributes to colorectal cancer (CRC) development through various interrelated mechanisms[7, 19, 20]. The gut microbiota, a dense and diverse microbial community, plays a pivotal role in maintaining gastrointestinal homeostasis[12, 13]. In obese individuals, this balance is disrupted, leading to a state of dysbiosis—a reduction in beneficial commensal microbes and an overgrowth of pathogenic species. Notably, obesity often results in a decreased Bacteroidetes-to-Firmicutes ratio and diminished populations of *Akkermansia muciniphila*, *Bifidobacterium*, and *Faecalibacterium prausnitzii*, species known for their anti-inflammatory and barrier-protective roles[21, 22].

This microbial imbalance compromises the intestinal epithelial barrier, increasing gut permeability and facilitating the translocation of bacterial products such as lipopolysaccharide (LPS) into the systemic circulation[23]. This condition, termed "metabolic endotoxemia," triggers chronic low-grade inflammation a hallmark of obesity. Adipose tissue in this inflamed state becomes metabolically active, secreting pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and adipokines (e.g., leptin, resistin) that further amplify systemic and local inflammation within the colonic mucosa[23]. These factors drive epithelial cell proliferation, suppress apoptosis, and create a pro-tumorigenic niche conducive to DNA damage and malignant transformation.

The gut microbiota contributes to CRC pathogenesis through multiple biological pathways. Immune modulation is a key mechanism—dysbiosis disrupts mucosal immune balance by impairing dendritic cell function, altering antigen presentation, and skewing the balance of T helper and regulatory T cells[24]. This facilitates immune evasion by neoplastic cells. Microbial metabolism also plays a role; harmful metabolites like secondary bile acids and trimethylamine-N-oxide (TMAO) increase, while protective metabolites such as short-chain fatty acids (SCFAs) decrease. Epigenetic modifications induced by microbial metabolites (e.g., butyrate, folate, polyamines) can alter gene expression profiles, influencing tumor suppressor gene activity[24, 25].

Given this complex interplay, modulating the gut microbiota presents a promising strategy for CRC prevention in obese individuals. Targeted interventions using prebiotics, probiotics, synbiotics, and dietary modifications may restore microbial balance, improve intestinal barrier integrity, and reduce inflammation, thereby mitigating CRC risk in this vulnerable population.

## 3. Key Gut Microbiota-Derived Metabolites in Obesity-Associated CRC

### 3.1 Short-Chain Fatty Acids (SCFAs)

SCFAs as primarily acetate, propionate, and butyrate, are metabolic end-products generated by the anaerobic fermentation of dietary fibers by commensal gut bacteria, such as *Roseburia*, *Eubacterium*, and *Faecalibacterium prausnitzii*[26]. Butyrate, in particular, plays a central role in colonic health. It is a primary energy source for colonocytes and serves as a signaling molecule that regulates various cellular processes. Butyrate exerts anti-inflammatory effects by inhibiting the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and reducing the expression of pro-inflammatory cytokines.[26, 27] Furthermore, it modulates gene expression through inhibition of histone deacetylases (HDACs), promoting cell cycle arrest, differentiation, and apoptosis in colorectal cancer cells.

Butyrate also enhances epithelial barrier function by upregulating tight junction proteins such as claudins and occludins[28]. It influences immune function by promoting regulatory T cell differentiation and suppressing inflammatory macrophage activity. However, in the context of obesity, SCFA production is markedly reduced due to several factors, including diminished fiber intake and depletion of SCFA-producing microbial species[28]. This reduction compromises mucosal immunity, promotes chronic inflammation, and increases susceptibility to CRC.

Therapeutic strategies aimed at restoring SCFA levels include increased consumption of fermentable fibers (e.g., inulin, resistant starch), administration of SCFA-producing probiotics, and supplementation with SCFA analogs[28]. Clinical studies have demonstrated that dietary interventions that increase butyrate production can improve epithelial health and reduce inflammatory markers in obese individuals[29]. These findings underscore the potential of SCFAs as therapeutic agents in CRC prevention and treatment, especially in metabolically compromised individuals.

### 3.2 Secondary Bile Acids

Secondary bile acids (SBAs) are microbial metabolites produced through the biotransformation of primary bile acids (PBAs) synthesized in the liver. In the gut, bacteria primarily from the *Clostridium* and *Eubacterium* genera convert PBAs such as cholic acid and chenodeoxycholic acid into SBAs like deoxycholic acid (DCA) and lithocholic acid (LCA)[30]. While bile acids are essential for lipid digestion and absorption, the excessive accumulation of SBAs, particularly in the colon, has been strongly associated with colorectal carcinogenesis.

DCA has been implicated in inducing oxidative stress, DNA damage, and genomic instability[31]. It promotes the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which directly damage cellular DNA, proteins, and lipids. Moreover, DCA activates pro-inflammatory signaling cascades such as nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), both of which enhance the expression of pro-tumorigenic cytokines and anti-apoptotic proteins[31]. DCA can also induce cellular proliferation via the Wnt/β-catenin and epidermal growth factor receptor (EGFR) pathways, thereby promoting tumor initiation and progression.

In obesity, bile acid homeostasis is profoundly disrupted. Increased dietary fat intake and insulin resistance stimulate hepatic bile acid synthesis via the classical CYP7A1 pathway[32]. At the same time, obesity-associated dysbiosis favors bacterial species with enhanced bile salt hydrolase and 7α-dehydroxylase activity, which accelerate the conversion of PBAs into carcinogenic SBAs. The cumulative effect is an elevated colonic concentration of DCA and LCA, contributing to mucosal injury, inflammation, and carcinogenesis[32].

Targeting bile acid metabolism has therapeutic potential in mitigating CRC risk. Dietary interventions such as reducing saturated fat intake and increasing fiber consumption can restore bile acid balance[33]. Certain probiotics like *Lactobacillus* and *Bifidobacterium* species have been shown to deconjugate and detoxify bile acids, reducing their carcinogenic potential. Additionally, pharmacologic agents such as bile acid sequestrants and farnesoid X receptor (FXR) agonists are under investigation for their ability to modulate bile acid signaling and reduce CRC progression[33]. Understanding the complex interplay between obesity, bile acid metabolism, and microbiota remains crucial for developing targeted CRC preventive strategies.

### 3.3 Indole Derivatives

Indole derivatives are a diverse group of microbial metabolites derived from the catabolism of the essential amino acid tryptophan by gut microbiota. Bacteria such as *Clostridium*, *Bacteroides*, and *Lactobacillus* convert tryptophan into bioactive compounds, including indole, indole-3-acetic acid (IAA), indole-3-aldehyde (IAld), and indole-3-propionic acid (IPA)[34]. These metabolites serve as important signaling molecules, particularly through their interaction with the aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor expressed throughout the gastrointestinal tract. Activation of AhR by indole derivatives promotes intestinal homeostasis by regulating epithelial cell proliferation, enhancing tight junction integrity, and suppressing pro-inflammatory responses[34]. IPA, for example, possesses potent antioxidant properties and protects against oxidative DNA damage in colonic epithelial cells. It also reduces the expression of inflammatory cytokines such as IL-6 and TNF-α, which are elevated in both obesity and CRC[35–37]. Moreover, indole derivatives support mucosal barrier function by stimulating mucin production and modulating immune responses, thereby preventing bacterial translocation and systemic inflammation.

In obesity, tryptophan metabolism is dysregulated due to altered gut microbiota composition. The abundance of beneficial tryptophan-metabolizing bacteria is reduced, leading to a decline in protective indole derivatives[38]. This shift contributes to increased intestinal permeability, chronic inflammation, and oxidative stress—factors that drive colorectal carcinogenesis. Additionally, metabolic syndrome and insulin resistance influence tryptophan catabolism through the kynurenine pathway, diverting it from microbial metabolism and exacerbating immune dysregulation[38]. Therapeutically, restoring indole derivative production holds significant promise. Strategies such as probiotic supplementation (e.g., *Lactobacillus reuteri*), dietary inclusion of tryptophan-rich or fiber-rich foods, and modulation of AhR signaling are being explored[39]. Additionally, emerging research highlights the role of microbial-host co-metabolism in the bioavailability and function of these compounds, suggesting personalized interventions based on individual microbiota profiles[39]. Understanding the mechanisms through which indole derivatives mediate gut-immune interactions provides a valuable framework for CRC prevention and therapy, particularly in the context of obesity-induced dysbiosis and inflammation.



### 3.4 Polyphenol Metabolites

Polyphenols are plant-derived compounds widely recognized for their antioxidant, anti-inflammatory, and anticancer properties[9, 40]. Major dietary sources include fruits, vegetables, tea, coffee, and wine. However, polyphenols are poorly absorbed in the small intestine; up to 90–95% reach the colon, where they are extensively metabolized by gut microbiota into smaller, bioactive phenolic metabolites[41, 42]. These metabolites, including urolithins, phenylpropionic acids, and hydroxycinnamic acids, exert potent biological effects relevant to colorectal cancer (CRC) prevention and management[43].

Microbial metabolism of polyphenols enhances their bioavailability and modulates their physiological activity. For instance, ellagitannins from pomegranates and berries are converted into urolithins, particularly urolithin A, which demonstrates anti-proliferative, pro-apoptotic, and anti-inflammatory effects in colon cancer cells[44]. Urolithin A also activates autophagy and improves mitochondrial function mechanisms that contribute to the elimination of damaged cells and the suppression of tumor initiation. Similarly, catechins from green tea and flavonoids from citrus fruits are transformed into phenolic acids that modulate signaling pathways such as NF-κB, PI3K/Akt, and MAPK, resulting in reduced inflammation and enhanced DNA repair[44].

In obesity, the metabolic capacity of the gut microbiota to transform polyphenols is compromised due to the depletion of key bacterial taxa such as *Gordonibacter*, *Slackia*, and *Eggerthella*. This alteration results in reduced production of beneficial metabolites and a diminished chemoprotective effect[45]. Additionally, increased oxidative stress and systemic inflammation in obese individuals may further attenuate the biological activity of polyphenol metabolites.

Interventions aimed at enhancing polyphenol metabolism include dietary diversification with polyphenol-rich foods, co-administration of specific probiotics, and development of polyphenol–microbiome synergy supplements[46]. Personalized nutrition strategies that consider the individual's microbiota profile can optimize the generation of bioactive metabolites and enhance CRC prevention [47]. Furthermore, synthetic biology approaches are being explored to engineer bacteria capable of efficient polyphenol bioconversion[46]. Altogether, gut microbial metabolism of dietary polyphenols represents a promising avenue for mitigating obesity-associated CRC risk, offering a natural and diet-based strategy to enhance mucosal defense, modulate inflammatory pathways, and prevent tumorigenesis.

## 4. Therapeutic Implications and Strategies

**4.1 Microbiota-Modulating Interventions**: Restoring gut eubiosis defined as a balanced and health-promoting microbial community, is an increasingly promising approach to reducing colorectal cancer (CRC) risk, particularly in obese individuals whose microbiota is often dysbiotic[48]. Several interventions are being explored to modulate the gut microbiota effectively. Prebiotics, such as inulin, fructooligosaccharides, and resistant starch, are non-digestible dietary fibers that selectively stimulate the growth of beneficial bacteria like *Faecalibacterium prausnitzii* and *Bifidobacterium* spp[49]. These bacteria enhance the production of short-chain fatty acids (SCFAs), especially butyrate, which has known anti-inflammatory and anti-carcinogenic properties. Probiotics, comprising live microorganisms such as *Lactobacillus* and *Bifidobacterium*, can competitively inhibit pathogenic bacteria, reinforce the intestinal barrier, and promote mucosal immune homeostasis[49]. Their administration has been associated with reduced tumor burden and improved gut integrity in preclinical models of CRC. Fecal Microbiota Transplantation (FMT) offers a more direct route by transferring stool from a healthy donor to a recipient with disrupted microbiota [50]. FMT has shown promise in treating Clostridioides difficile infections and is currently being evaluated for efficacy in CRC prevention[49]. By re-establishing microbial balance, FMT can reintroduce beneficial metabolic functions and reduce inflammation-driven tumorigenesis. Although still under investigation, these microbiota-modulating strategies underscore the therapeutic potential of targeting the gut ecosystem as a preventive and adjunctive approach in obesity-associated colorectal cancer.

**4.2 Metabolite-Based Therapies**: Targeting microbial metabolites represents a novel and potentially transformative therapeutic avenue in obesity-associated colorectal cancer (CRC). Certain microbial-derived compounds possess immunomodulatory, anti-inflammatory, and anti-tumor properties that can be leveraged to counteract the carcinogenic effects associated with dysbiosis[51]. One of the most studied metabolites is butyrate, a short-chain fatty acid (SCFA) produced predominantly by *Faecalibacterium* and *Roseburia* species through the fermentation of dietary fiber[52]. Butyrate acts as a histone deacetylase (HDAC) inhibitor, promoting apoptosis and inhibiting the proliferation of colon cancer cells. Butyrate enemas have demonstrated chemopreventive effects in experimental models of colitis-associated CRC by restoring epithelial barrier function and dampening pro-inflammatory cytokine production. Another promising class of metabolites includes indole derivatives produced from dietary tryptophan by gut microbiota[52]. These compounds activate the aryl hydrocarbon receptor (AhR), a transcription factor involved in maintaining mucosal homeostasis and regulating immune responses. AhR agonists such as indole-3-aldehyde and indole-3-propionic acid exhibit anti-inflammatory effects and are under investigation for their ability to modulate T-cell responses and suppress tumor-promoting inflammation. Additional compounds under study include secondary bile acids, polyamines, and conjugated linoleic acids, although their dual roles in cancer promotion and suppression necessitate precise modulation. Metabolite-based therapies thus offer a precision-medicine approach to CRC prevention and treatment, allowing the use of naturally occurring or synthetically derived analogs to restore microbial functionality, modulate immunity, and directly affect tumor biology without the need for systemic antibiotics or major dietary overhauls[52].



### 4.3 Diet and Lifestyle Modifications

Dietary and lifestyle interventions represent foundational strategies for modulating the gut microbiota and reducing the risk of obesity-associated colorectal cancer (CRC). Diets high in fiber, polyphenols, and fermented foods have been shown to favor the proliferation of beneficial gut bacteria and the production of protective microbial metabolites such as short-chain fatty acids (SCFAs)[53]. Fiber-rich diets, especially those containing whole grains, legumes, fruits, and vegetables, enhance butyrate production, which in turn supports colonic epithelial health and exerts anti-inflammatory and anti-carcinogenic effects[53]. Polyphenol-rich foods, such as berries, green tea, cocoa, and olive oil, act as prebiotics and antimicrobial agents, shaping microbial composition while simultaneously modulating redox status and inflammatory pathways. Fermented foods like yogurt, kefir, kimchi, and sauerkraut are natural sources of probiotics that contribute to microbial diversity and gastrointestinal resilience[54]. Dietary patterns such as the Mediterranean and plant-based diets offer a composite benefit by integrating these elements into a sustainable lifestyle model[54]. These diets are consistently associated with reduced systemic inflammation, improved metabolic health, and lower cancer incidence through favorable shifts in the microbiota-metabolite axis. Beyond diet, physical activity, sleep hygiene, and stress reduction also influence gut microbial diversity and systemic immune function[55]. Sedentary lifestyles and chronic stress are linked to dysbiosis and increased CRC risk, whereas regular physical activity has been shown to enrich microbial diversity and enhance SCFA levels[55]. Taken together, comprehensive diet and lifestyle modifications offer a non-invasive, cost-effective, and holistic approach to CRC prevention by targeting both metabolic and microbial pathways involved in obesity-related carcinogenesis.

## 5. Conclusion and Future Directions

The gut microbiota and its natural metabolites serve as a critical nexus linking obesity and colorectal cancer. Understanding the metabolic outputs of gut microbes and how they interact with host pathways opens up new frontiers for personalized medicine. Therapeutic strategies targeting microbiota-derived metabolites, whether through diet, probiotics, or direct metabolite supplementation, represent promising adjuncts in preventing and treating CRC, particularly in the context of obesity.

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