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REVIEW ARTICLE

# Investigating the Influence of Gut Microbiota-related Metabolites in Gastrointestinal Cancer

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**Abstract:** Gastrointestinal (GI) cancer is a major health concern due to its prevalence, impact on well-being, high mortality rate, economic burden, and potential for prevention and early detection. GI cancer research has made remarkable strides in understanding biology, risk factors, and treatment options. An emerging area of research is the gut microbiome's role in GI cancer development and treatment response. The gut microbiome, vital for digestion, metabolism, and immune function, is increasingly linked to GI cancers. Dysbiosis and alterations in gut microbe composition may contribute to cancer development. Scientists study how specific bacteria or microbial metabolites influence cancer progression and treatment response. Modulating the gut microbiota shows promise in enhancing treatment efficacy and preventing GI cancers. Gut microbiota dysbiosis can impact GI cancer through inflammation, metabolite production, genotoxicity, and immune modulation. Microbes produce metabolites like short-chain fatty acids, bile acids, and secondary metabolites. These affect host cells, influencing processes like cell proliferation, apoptosis, DNA damage, and immune regulation, all implicated in cancer development. This review explores the latest research on gut microbiota metabolites and their molecular mechanisms in GI cancers. The hope is that this attempt will help in conducting other relevant research to unravel the precise mechanism involved, identify microbial signatures associated with GI cancer, and develop targets.

**Keywords:** Microbiota-derived metabolites, gastrointestinal cancer, dual role, gut microbiota, gut microbiota dysbiosis, metabolite production.

## 1. INTRODUCTION

Despite significant advancements in cancer treatment, it remains the second leading cause of death globally, accounting for up to 10 million deaths in 2021 [1, 2]. Among all cancer types, gastrointestinal (GI) neoplasms are considered one of the most aggressive and fatal tumors, responsible for approximately one-third of cancer-related deaths [3]. The development of GI cancers is believed to be influenced by a combination of genetic and environmental factors, as well as lifestyle choices. However, the precise mechanisms underlying GI carcinogenesis have not been fully elucidated [4]. The complexity of cancer pathogenesis often hampers the effectiveness of conventional therapeutic options, necessitating the exploration of novel approaches [5]. A more comprehensive grasp of the associated contributions will lead to increasingly successful treatment outcomes. Recently, emerging research has identified a potential link between gut microbiota and cancer [6]. The gut microbiota comprises a diverse community of bacteria residing in the digestive system [7]. The majority of microbial populations are concentrated in the GI tract, with an estimated population exceeding $10^{14}$ bacteria, primarily in the large intestine [8, 9]. The most prevalent bacterial genera constituting the gut microbiota include *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* [10]. These bacteria produce various metabolites, such as bile acids (BAs), short-chain fatty acids (SCFAs), choline, Trimethylamine-N-oxide (TMAO), and polyamines (PAs), either from dietary sources or host compounds [11]. These metabolites play crucial roles in vitamin production (*e.g.,* K and B), immune modulation, mucosal barrier protection, and inhibition of pathogenic bacterial growth [12, 13]. However, disruption of the microbiota balance, known as dysbiosis, can increase the risk of various disorders, including irritable bowel syndrome (IBS), rheumatoid arthritis, obesity, inflammatory bowel disease (IBD), and cancers, by impairing the normal functioning of the immune system [14-17]. When it comes to cancers, evidence suggests that microbial imbalances are associated with approximately 20% of GI cancers [18]. On the other hand, the impact of microbial metabolites on GI cells is strongly influenced by diet and microbial composition. For instance, a high intake of plant-based foods has been shown to increase the abundance of *Prevotella*, *Lactobacil-*

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