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MICROBIOTA -MEDIATED METABOLISM AND PROBIOTICS INTERVENTIONS IN COLORECTAL CANCER: A REVIEW

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Abstract:

The gut microbiota modifies drugs, impacting their effects through chemical changes. Recent research uncovers complex microbe-drug interactions that can alter treatment outcomes. Drugs and the gut microbiome can mutually affect each other, changing drug processing and effects.Therapeutic drugs and xenobiotics can alter the gut microbiome's makeup and functions. These changes can affect how drugs are chemically transformed, influencing treatment outcomes.Colorectal cancer (CRC) is a prevalent and lethal disease, linked to factors like genetics and lifestyle. Current treatments often lead to negative effects, affecting patients' well-being. Probiotics have emerged as a promising approach to alleviate treatment side effects and enhance the health of CRC patients.The review discusses microbial drug modification genetics, drug effects on gut microbes, and the gut microbiota's involvement in drug metabolism and how probiotics can improve CRC patient's condition by bolstering gut health, releasing protective substances, and enhancing intestinal functions. The effectiveness of probiotics depends on factors such as strain selection, dosage, and individual physiology. Identifying potent probiotic strains is essential for developing targeted CRC therapies.

Keywords: Gut microbiome,Xenobiotics, Colorectal cancer, Probiotics, Drug metabolism.

Introduction:

The intricate community of microorganisms in the human gut is closely linked to vital processes such as nutrient synthesis, digestion, immune development, and preventing unwanted microbes (Morowitz MJ *et al*, 2011).New findings show that the gut microbiota play a significant role in metabolizing orally ingested xenobiotics, such as environmental pollutants, dietary elements, and medicines. The primary bacterial phyla in the human gut comprise Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia (Magne F *et al*, 2020).Diet, age, and health impact the proportions of these phyla .The gut microbiota possesses approximately 3.3 million distinct genes, significantly outnumbering human genes (Liu et al., 2006) This extensive enzymatic potential, exceeding that of the liver, allows the gut to metabolize drugs and xenobiotics, influencing their effects on the body (Koppel N *et al*, 2017).

The role of particular gut bacteria and their genetics in xenobiotic processing is still developing. Studying this process and individual differences could enhance treatment approaches. Targeting microbial functions involved in xenobiotic metabolism may improve drug effectiveness and diagnostics. These genetic markers could also contribute to the progress of precision medicine.This paper presents a summary of how gut microbes alter therapeutics, affecting health and disease, both directly and indirectly. We focus on the complex interplay between

gut microbiota functions and xenobiotics. Our evaluation centers on the genetic makeup and metabolic activities of the human gut's microbial population. Additionally, we review the current understanding of how these microbial communities create chemical changes in xenobiotic conjugates, drugs, and prodrugs.

Xenobiotics and Their Metabolic Processes-

Xenobiotics encompass substances that are non-native to the human body (Qadir A *et al,* 2017).Xenobiotics are divided into two types: exogenous, which include synthetic compounds from diet, drugs, and pollutants like pesticides; and endogenous, produced within the body like steroids and fatty acids. High quantities of certain substances are also termed xenobiotics.Xenobiotics pose risks in the human body and the environment, with potential for carcinogenic effects, toxicity, accumulation, and prolonged presence in fatty tissues, contributing to chronic issues such as cancer (Harrison PTC *et al,* 1995).Xenobiotics undergo intricate transformations in the stomach's acidic environment, involving microbial and host enzymes. Gut microbes also metabolize dietary compounds, impacting health and disease. Orally ingested xenobiotics are modified by both microbes and host enzymes before entering circulation. These modified substances can influence bioactivity, bioavailability, and toxicity. The anaerobic intestine aids digestion by metabolizing indigestible compounds into short-chain fatty acids, which regulate metabolism (Archana Pant *et al,* 2022).

Colorectal cancer (CRC) stands as a widespread malignancy, with roughly 1.4 million cases in 2012 and causing about 700,000 deaths. Various elements, such as unhealthy lifestyles, diet, genetics, heredity, and metabolic disruptions, are linked to CRC occurrence (Johns L *et al,* 2001).Around 70% of CRC cases are attributed to environmental factors, and its occurrence has surged in technologically advanced nations due to decreased physical activity (Rossi M *et al,* 2018).The gut microbiota has a close connection to CRC incidence and advancement. Altered gut microbiota can trigger cancer development by influencing immune responses, cell function, metabolism, DNA damage, and molecular activities in colon cells. Although advanced treatments such as chemotherapy, surgery, immune therapy, and radiation are accessible for CRC, survival rates remain modest, often accompanied by adverse side effects that diminish quality of life (Hendler R *et al,* 2018). Administering sufficient probiotics offers health benefits by positively influencing the gut microbiota. Imbalance in the microbiota is a significant factor in CRC development. Studies suggest that probiotics can protect CRC patients from treatment-related adverse effects, demonstrating advantages over control groups in various research (Krebs B *etal,* 2016).A strong probiotic strain plays a crucial role in preventing tumorigenesis, including CRC, by engaging in activities such as competing for adhesion sites, producing microbicidal agents like bacteriocin, improving intestinal permeability, releasing bioactive metabolites, regulating immune pathways, and stimulating protective cellular responses (Hendler R *et al,* 2018).

Unveiling a Potential Mechanism for Probiotics and Their Derivatives in Combating CRC-

Despite numerous studies aiming to clarify the mechanism behind the anticarcinogenic effects of probiotics,the precise mechanism underlying probiotics' anti-CRC activity remains elusive. However, multiple clues indicate that probiotics enhance health by modifying microbiota composition and metabolic functions, producing anticarcinogenic and antimicrobial substances, bolstering host antioxidant defenses, metabolizing carcinogens, influencing inflammation-related gene expression, boosting immunity, and inhibiting cancer cell proliferation and apoptosis (Faghfoori Z *et al,* 2015).

Bacterial enzymes produced by organisms such as Clostridium, Bacteroides, and Eubacterium, including nitrate reductase, azoreductase, β-glucosidase, β-glucuronidase, and 7-α-dehydroxylase, contribute to the formation of carcinogenic compounds like cresols, ammonia, phenols, aglycones, and N-nitroso compounds. These compounds trigger antiapoptotic pathways, supporting the development of CRC (Tjalsma H *et al,* 2012).

The addition of probiotics improves the integrity of the gut barrier. Three crucial factors—pH, tight junction proteins, and secreted mucins—safeguard the intestinal epithelial lining. Probiotics' metabolic processes produce organic acids and SCFAs, helping maintain a favorable low pH in the intestinal lumen (Liu J.-R *et al,* 2006). The

host's protection against cellular damage and subsequent diseases involves its antioxidant system, as it combats free radicals. Various studies indicate that probiotic supplementation enhances the host's antioxidant capability. This supplementation also impacts host physiology, influencing factors like polyamine regulation and ornithine decarboxylase enzyme activity, thereby reducing the risk of CRC development (Milovic V. *et al*, 2003).

Research has unveiled that probiotic microorganisms have the ability to inhibit the growth of cancer cells and trigger apoptosis. This effect is primarily linked to the production of short-chain fatty acids (SCFAs) (Sadeghi-Aliabadi H et al, 2014).

Multiple factors, including the specific probiotic strain, its concentration, viability, consumption duration, and supplementation with prebiotic fibers, can impact the mechanisms we've discussed. As a result, not all probiotic strains exhibit anti-CRC properties. Therefore, it is crucial to meticulously screen and select potent strains for the development of probiotic-based therapies to effectively control or prevent CRC incidence.

Conclusion-

In summary, the intricate realm of utilizing probiotics to address CRC-related mechanisms underscores the multifaceted dynamics influenced by a range of critical factors. These factors encompass the distinct attributes of the chosen probiotic strain, its concentration within the formulation, the preservation of viability throughout consumption, the duration over which probiotics are administered, and the potential synergistic effects achieved through the addition of prebiotic fibers.

Our investigation makes it evident that not all probiotic strains inherently possess the capability to counter CRC-associated processes. This underscores the imperative of a comprehensive and meticulous screening process to identify and isolate potent strains that exhibit the desired anti-CRC properties. This discerning approach forms the cornerstone for developing tailored therapeutic strategies based on probiotics, which hold the potential to significantly control or even preempt the occurrence of CRC.

Ultimately, harnessing probiotics as a tool to combat CRC necessitates a nuanced consideration of the intricate interplay among strain attributes, formulation specifics, and therapeutic outcomes. By judiciously selecting and utilizing the most effective probiotic strains, we stand at the threshold of a promising realm in the fight against CRC. This opens avenues for innovative and precisely targeted interventions that could make a substantial impact on the course of this prevalent and impactful disease.

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