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MINI-REVIEW

The relationship between fermented foods and colorectal cancer: A review

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Abstract

Despite advancements in medical technology, cancer remains a leading cause of mortality, with colorectal cancer consistently ranking among the most prevalent cancers worldwide. Diet can either contribute to or protect against the development of cancer. The Asian region is known for its extensive consumption of fermented foods, which may influence colorectal cancer due to the diverse range of microorganisms and compounds produced during fermentation. These components can affect the tumor microenvironment, potentially leading to either beneficial or adverse effects on colorectal cancer.

Keywords: Colorectal cancer; Fermented foods; Cell; Animal

1. Introduction

Cancer is a significant contributor to global mortality. According to recent data from the World Health Organization, around one out of every six deaths in 2020 was attributed to cancer.[1,2] In its early stages, cancer is manageable and can be treated and prevented using medications, herbal remedies, and other therapeutic approaches.[3,4] Nevertheless, the most alarming aspect lies in the ability of malignant cells to spread and proliferate, breaching barriers and infiltrating adjacent tissues.[5] This process, known as metastasis, is the primary cause of cancer-related deaths.[6,7] Numerous elements contribute to the development of cancer, with heredity and environmental exposure being among the most prominent.[8,9] However, the living environments of most cancer patients do not necessarily contain significant carcinogenic elements.[10-12] Instead, poor dietary habits and nutritional factors often play a more crucial role, such as the established associations between tobacco and lung cancer, alcohol and liver cancer, and other similar links.[8,13-15] It is difficult to deny the inherent connection between lifestyle factors and cancer incidence.

Colorectal cancer ranks third in terms of the number of cases but is the second leading cause of cancer-related mortality worldwide.[16] Diet is considered one of the key contributing factors to the development of colorectal cancer.[15,17] This is not surprising, as the food we consume is processed and absorbed in the intestines, which serve as the primary site of nutrient metabolism.[18,19] The intestinal environment is complex, comprising a diverse array of microbes and metabolites.[20,21] Several dietary components have been implicated in the development of colorectal cancer, including ultra-processed foods, dietary microplastics, aflatoxins in fermented products, and diets high in sugar and fatty meats.[22-25]

Fermentation is a biochemical process in which bacteria and enzymes act on raw materials, resulting in specific or non-specific physical and chemical transformations that ultimately produce distinct food products.[26] During fermentation, the selection of microorganisms and the control of fermentation time are carefully managed to ensure that the resulting product possesses unique nutrients and flavors, as seen in soy sauce and vinegar.[27-29] In some cases, it is essential to pre-mix specific combinations of microorganisms and enzymes.[30] This mixture is then fermented for a specific duration, followed by a secondary fermentation of the raw materials.[31] This process further enhances the complexity of composition and flavor, as observed in products such as *baijiu*, tea, and gammon.[32] Depending on the raw materials used, fermented products can be broadly categorized into fermented beans, dairy, meats, grains, and other related items.[33] Through microbial fermentation, these foods can generate diverse beneficial bacteria and bioactive metabolites while preserving their inherent nutrients.[34,35] This has significant positive implications for the treatment of colorectal cancer.

Colorectal cancer exhibits significant variation in both incidence and mortality rates across different geographical regions.[36] Europe, Australia, and New Zealand, which are considered developed regions, report the highest incidence rates,[37] while Eastern Europe has the highest mortality rates associated with the disease.[38] In contrast, Asian regions like China and India demonstrate lower incidence rates, which may be attributed to local dietary patterns.[39] Regions in China with low incidence rates, such as Guizhou, as well as Japan and South Korea, rely heavily on fermented foods as essential components of their daily diets.[40,41] These include products like soy sauce, vinegar, *baijiu*, kimchi, and marinated fish fillets. This implies that while screening in high-income areas contributes to earlier prevention of colorectal cancer, diet remains a significant contributing factor.[42] Yogurt, a common fermented product made using lactic acid or yeast, has a notable impact on enhancing intestinal ecology and reducing the risk of colorectal cancer.[43] Fermented legumes contain peptides and other compounds known to possess properties that suppress the development of colorectal cancer.[44,45]

The following sections of this review focus on examining the impact of fermented foods on colorectal cancer by analyzing the relationship between bacterial flora and intestinal flora, the presence of bioactive compounds and metabolites in fermented foods, and current research methodologies. The aim is to organize and trace these concepts and approaches to support the development and application of high-throughput evaluation techniques for studying the role of fermented foods in colorectal cancer.

2. Association between different traditional fermented foods and cancer

2.1. Role of fermented foods in colorectal cancer prevention through gut flora modulation

The dysregulation of the intestinal microbiota can directly facilitate the initiation and progression of colorectal cancer by inducing inflammation in the intestines, compromising the intestinal barrier, and causing immune system dysfunction.[46,47] Chen *et al.*[51] conducted a comprehensive assessment of the efficacy and safety of probiotics as a supplementary treatment for colorectal cancer. Their findings indicate that probiotics can influence the physiological and immune mechanisms of the host, potentially contributing to the regulation of anti-tumor activity. Gomaa[49] demonstrated that probiotics can modulate intestinal dysbiosis, thereby promoting host health.

The key component of fermented foods is the microorganisms introduced during the fermentation process. It is also vital to investigate the microbial composition of fermented foods at various stages of fermentation. Probiotics are among the by-products of fermented foods once fermentation is complete. Notably, studies have demonstrated that *Lactobacillus* spp. and *Bifidobacterium* spp., which are the predominant types of probiotics, have the ability to improve gastrointestinal function and strengthen the immune system of the intestinal tract.[50] *Lactobacillus* and *Bifidobacterium* can directly interact with immune cells. *Lactobacillus* may increase anti-inflammatory cytokines (i.e., interleukin [IL]-10 and IL-12) and upregulate caspase-7 and caspase-9, thus enhancing apoptosis. It may also reduce levels of pro-inflammatory cytokines (i.e., tumor necrosis factor-α, interferon-γ, IL-1β, and IL-6) and inflammation-related enzymes such as inducible nitric oxide synthase and cyclooxygenase-2. *Bifidobacterium* regulates the proliferation of T cells and B cells and affects T helper (Th) 1/Th2 cytokine balance. *Lactobacillus* spp. and *Bifidobacterium* spp. are commonly found in fermented products like yoghurt. *Lactobacillus* primarily influences the intestinal environment by modulating inflammatory markers.[51] Sugimura *et al.*[52]

found that it can alter the intestinal microenvironment in patients undergoing chemotherapy for colorectal cancer. *Clostridium butyricum*, a butyrate-producing bacterium, also contributes to intestinal flora balance.[53] It has been shown to inhibit intestinal tumor development by modulating Wnt signaling. Maintaining this microbial balance helps limit tumor growth and promotes apoptosis, the programmed death of cancer cells.

2.2. Prevention of colorectal carcinogenesis by beneficial components produced during fermentation

Fermented food generates a variety of beneficial metabolic compounds such as peptides and short-chain fatty acids during fermentation (Table 1).[54] These substances have the potential to suppress the development of colorectal cancer. Microorganisms ferment soybeans to produce valuable compounds such as soy polypeptides, soy isoflavones, soy oligosaccharides, and others.[55] These components possess antioxidant, digestive, and anticancer properties. Probiotic metabolites and their derivatives exhibit biological properties, including the inhibition of cancer cell growth, promotion of cancer cell apoptosis, and regulation of the immune response.[56] *Lactobacillus plantarum* and its metabolite, indole 3-lactic acid, enhance intestinal health by reducing inflammation, inhibiting tumor growth, restoring microbial balance, boosting immune responses, and exerting anti-tumor effects.[57] Butyrate demonstrates anticancer properties by increasing the expression of short-chain fatty acid transporter protein solute carrier family 5 member 8 and G protein-coupled receptor 43 in the epithelial cells and lamina propria cells of mouse colon tumors.[58] Ferulic acid, a compound found in large quantities in fermented foods, effectively prevents the development of colorectal cancer in both living organisms and laboratory settings by targeting crucial pathways in colorectal cancer cells.[59] Extracellular polysaccharides prevent pathogens from adhering to the intestinal epithelium, enhance intestinal barrier integrity, and regulate mucosal immune responses.[60] Short-chain fatty acids suppress colorectal cancer cell growth and induce programmed cell death.[61] The Western dietary pattern, considered unhealthy, has been linked to an increase in secondary bile acids in the intestines, including deoxycholic acid and lithocholic acid.[62] Elevated levels of bile acids have been strongly associated with a high incidence of colorectal cancer.[52] Although alcohol is recognized as a carcinogen, the fermentation process of beer and Chinese *baijiu* produces substances like 4-methylguaiacol, which contribute both to flavor and potential health benefits.[63,64] These substances, despite being present in small amounts alongside alcohol, have demonstrated cancer-inhibiting effects.

2.3. Research techniques for studying fermented foods and colorectal cancer

Colorectal cancer is a significant public health issue, and individual variations among patients have a considerable impact on its development.[66] Consequently, examining

Table 1. Metabolic compounds and functions

No.	Compound	Function	Source
1	Extracellular polysaccharides	Enhance gut barrier function; prevent pathogen attachment	Tang *et al.*[22]
2	Bile acids	Aid in fat digestion and absorption; certain secondary bile acids are linked to colorectal cancer	Lamaziere *et al.*;[44] Liu *et al.*[56]
3	Peptides	Act as signaling molecules; regulate cell growth, differentiation, and metabolism	Ashaolu *et al.*[55]
4	Short-chain fatty acids	Maintain gut health, provide energy, and regulate immune responses	Ashaolu *et al.*[55]
5	Soy polypeptides	Exhibit antioxidant activity; contribute to blood pressure reduction	Kim *et al.*[50]
6	Soy isoflavones	Possess antioxidant, anticancer, and hormone-regulating effects	Kim *et al.*[50]
7	Soy oligosaccharides	Function as prebiotics; promote the growth of beneficial gut bacteria	Kim *et al.*[50]
8	Butyrate	Supports gut epithelial health and function; exhibits anticancer properties	Hajjar *et al.*[65]
9	Ferulic acid	Demonstrates antioxidant and anticancer effects; prevents the development of colorectal cancer	Chen *et al.*[39]
10	Indole-3-lactic acid	Exhibits anti-inflammatory and anticancer activities	Zhang *et al.*[59]
11	4-methylguaiacol	Offers antioxidant and anticancer effects	Qiao *et al.*;[64] Liao *et al.*[41]

the etiology of colorectal cancer across different patient populations often yields conflicting findings.

In the early stages of colorectal cancer research, both domestic and international scholars have typically employed extensive epidemiological investigations to explore contributing factors.[67-69] For instance, by utilizing resources such as GenBank and other databases, researchers can effectively examine the impact of various age groups or dietary factors on colorectal cancer in a relatively straightforward manner.[65,70] Epidemiological surveys offer a more objective approach to investigating and assessing the causes of colorectal cancer.[50] However, this method is limited by the need for large sample sizes and diverse sample sources. In addition, it is often constrained by the limitations of existing research databases, making it challenging to accurately assess the relationship between a particular food or treatment and colorectal cancer, as well as to identify precise mechanisms of action. With the growing popularity of bioinformatics, network pharmacology has become a widely used technical tool for studying potential treatments for colorectal cancer.

In recent years, due to advancements in life science research methods, an increasing number of researchers, both in China and internationally, have evaluated colorectal cancer treatments using animal or cell model systems. Lee *et al.*[71] assessed the anticancer effects of regular kimchi and concentrated kimchi fermented for varying durations on HT-29 colorectal cancer cells. The results indicated that kimchi with a longer fermentation period had a more potent anticancer activity. Kumari *et al.*[72] examined how the antiproliferative activity of soymilk could be enhanced by fermenting it with different bacterial agents. They found that fermentation effectively improved soymilk's ability to inhibit the growth of colorectal cancer cells. Fermented products derived from traditional Chinese medicine raw materials also demonstrated antiproliferative activity against colorectal cancer cells, which was dependent on both dosage and duration of exposure.[73]

Animal experiments are particularly effective in determining the impact of various chemical doses on colorectal cancer. Chen *et al.*[39] identified the optimal dosage of ferulic acid as a colorectal cancer suppressor using an *in situ* implantation tumor model. The inclusion of a diet containing 10% *Aspergillus oryzae*-fermented brown rice was found to inhibit the spread of cancer cells in mice injected with colorectal cancer cells.[71] Fermented soy sauce also showed protective effects on the colon and inhibited cancer cell growth.[72]

In summary, when evaluating the health effects of specific fermented foods, animal and cellular models offer greater precision compared to epidemiological surveys and network pharmacological analyses. Combining these approaches may offer a valuable direction for future research.

3. Conclusion

Fermented foods are increasingly gaining attention due to their distinct flavors and diverse array of health-promoting compounds. A multitude of studies has consistently demonstrated that diet plays a crucial role in the development of colorectal cancer. Consuming fermented foods in moderation may help lower the risk of cancer. However, it is important to note that the potential reduction in risk may be limited due to the relatively low levels of various types of probiotics and other beneficial substances found in fermented foods. Therefore, fermented foods alone are unlikely to reach the minimum threshold required for the effective treatment of colorectal cancer. Nevertheless, fermented foods contain a diverse range of short-chain fatty acids and powerful probiotics. Their ability to combat cancer involves multiple simultaneous pathways, including the induction of apoptosis and autophagy, inhibition of cell proliferation, activation of oncogenes, and potentially safeguarding healthy cells through enhanced anti-inflammatory and antioxidant mechanisms. Based on the existing evidence, fermented foods have been shown to have a substantial positive impact on lowering the occurrence of colorectal cancer. However, further clinical research is necessary to establish a more conclusive and direct correlation.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

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