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Kombucha and Colorectal Cancer: Unraveling the Microbiota-Metabolite-Host Axis as a Potential Mechanism for Prevention and Therapy

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Abstract

Purpose: This review evaluates the potential role of kombucha in Colorectal Cancer (CRC) prevention and adjunctive therapy through the microbiota–metabolite–host axis, emphasizing bioactive compounds, fermentation metabolites, gut microbiota, oxidative-inflammatory pathways, immune responses, and carcinogenesis.

Methods: A review of studies published between 2015 and 2025 was conducted using PubMed, ScienceDirect, and Google Scholar. Experimental, preclinical, clinical, and review evidence on kombucha, fermented tea, microbiota, microbial metabolites, probiotics, prebiotics, oxidative stress, inflammation, CRC, and anticancer mechanisms was synthesized.

Results: Kombucha may modulate the gut microbiota, metabolism, oxidative stress, inflammation, immunity, proliferation, and apoptosis through its bioactive compounds. However, evidence for the prevention or treatment of CRC remains largely preclinical.

Conclusions: Kombucha may provide a mechanistic basis for investigating its use as a dietary adjunct for CRC prevention and supportive care; however, its therapeutic efficacy requires confirmation in human studies.

Limitations: Evidence is limited by heterogeneous fermentation conditions, composition, microbial communities, metabolite profiles, insufficient strain-specific characterization, and scarce standardized human interventions.

Contributions: This review integrates kombucha evidence within a microbiota–metabolite–host framework, connecting fermented tea bioactives, microbial ecology, metabolite signaling, intestinal homeostasis, and CRC pathways, while identifying priorities for metabolomic, microbiome, mechanistic, and clinical research.

Keywords: *Bioactive Compounds, Colorectal Cancer, Gut Microbiota, Kombucha, Microbial Metabolite*

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1. Introduction

Colorectal Cancer (CRC) is a malignancy that develops in the epithelium of the colon and/or rectum and represents one of the major global health problems, carrying a substantial burden of morbidity and mortality. According to the latest global estimates, CRC ranks third among the most frequently diagnosed cancers and is the second leading cause of cancer-related deaths worldwide. In 2022, more than 1.9 million new CRC cases were diagnosed, and more than 900,000 deaths were attributed to the disease. More recent GLOBOCAN data further indicate that CRC continues to contribute substantially to the global cancer burden, accounting for approximately 9.9% of all new cancer cases and 9.4% of cancer deaths in 2024. This high burden underscores that CRC remains an important challenge for health systems despite advances in screening, early detection, surgery, systemic therapy, and molecularly targeted therapy.

In Indonesia, GLOBOCAN 2022 estimated age-standardized CRC incidence and mortality rates of 15.7 and 8.9 per 100,000 population, respectively. Demographic transition, urbanization, diet, obesity, physical inactivity, alcohol, tobacco, and other metabolic factors may contribute to this burden. Tobacco is a documented cancer risk factor, and awareness of smoking warnings may shape preventive behaviors among young people (Marselin, 2025). Therefore, CRC control requires both effective treatment and biologically grounded prevention. CRC develops through the accumulation of genetic, epigenetic, metabolic, and microenvironmental alterations. Dysregulation of the Wnt/β-catenin, RAS-RAF-MEK-ERK, PI3K-AKT, and TGF-β pathways affects proliferation, differentiation, survival, apoptosis, invasion, and tumor progression (Li et al., 2024). Most CRC cases are sporadic, while a minority involve hereditary conditions, such as Lynch syndrome and familial adenomatous polyposis. Carcinogenesis may follow the conventional adenoma-carcinoma sequence or serrated pathway, which is associated with BRAF/KRAS mutations, CpG island methylator phenotype, and sometimes mismatch-repair loss and microsatellite instability. These routes reflect interactions among genetic, epigenetic, environmental, and intestinal factors (Li et al., 2024).

CRC pathogenesis also involves the intestinal ecosystem. Gut microbial alterations may affect inflammation, DNA damage, immunity, metabolism, and tumorigenesis (White and Sears, 2024). However, microbiome associations are influenced by transit time, inflammation, body mass index, diet, medication, and clinical characteristics (Ray 2024; Tito et al. 2024). Therefore, interpretation should emphasize microbial function and host interactions rather than individual taxa. Microbial metabolites link the gut microbiota with carcinogenesis by affecting epithelial and immune function, inflammation, oxidative stress, barrier integrity, epigenetic regulation, and cellular signaling. Short-Chain Fatty Acids (SCFAs), particularly butyrate, may support epithelial homeostasis and immune regulation, whereas some secondary bile acids and genotoxins may promote inflammation and carcinogenesis (Louis et al., 2014; Turocy & Crawford, 2025). Evidence supports the beneficial role of butyrate in CRC prevention and supportive care (Kaźmierczak-Siedlecka et al., 2022; Liu et al., 2024), although heterogeneous associations between fecal SCFAs and CRC limit causal inference (Alvandi et al., 2022).

The microbiota-metabolite-host framework explains how diet modifies microbial composition and function, how microorganisms transform substrates into metabolites, and how these metabolites influence epithelial homeostasis, immunity, inflammation, metabolism, and the tumor microenvironment. Therefore, it supports the investigation of kombucha, a fermented tea containing microorganisms, polyphenols, organic acids, and fermentation-derived metabolites, as a complementary CRC intervention. Kombucha is produced by fermenting sugared tea (Camellia sinensis) with a Symbiotic Culture of Bacteria and Yeast (SCOBY). Fermentation alters tea polyphenols and generates new metabolites. SCOBY commonly contains acetic acid bacteria and yeasts; however, its composition varies with the starter, substrate, environment, conditions, and duration (Esatbeyoglu et al., 2024; Marco et al., 2021).

During kombucha fermentation, yeasts metabolize sucrose, while acetic acid bacteria convert the resulting substrates into organic acids and other compounds. Therefore, the final product is a variable matrix of tea components, microorganisms, and microbial biotransformation products that may

interact with the gastrointestinal environment (Esatbeyoglu et al., 2024; Marco et al., 2021; Salminen et al., 2021). Kombucha should not be automatically considered a probiotic. The International Scientific Association for Probiotics and Prebiotics defines probiotics as adequately characterized live microorganisms that confer demonstrated health benefits at appropriate doses (Hill et al. 2014). Because kombucha microorganisms and their benefits vary by product and process, probiotic status requires product- and strain-specific evidence (Marco et al., 2021). Kombucha may affect gut microbiota and host metabolism through interactions among microorganisms, fermentation metabolites, and tea bioactives; however, the evidence remains largely preclinical and heterogeneous in terms of substrate, composition, dose, and method (Costa et al., 2023; Esatbeyoglu et al., 2024). A small trial in patients with type 2 diabetes showed a metabolic effect, but could not establish cancer prevention or treatment (Mendelson et al., 2023). Standardized human studies are required to confirm these findings.

In CRC, altered microbial communities may change the levels of SCFAs, bile acid metabolites, and other molecules that influence barrier integrity, inflammation, oxidative stress, epigenetic regulation, proliferation, and cell death. In turn, host metabolic and inflammatory conditions can reshape the microbiota. This multidirectional microbiota-metabolite-host axis links diet, microbiome, metabolism, and CRC (Louis et al., 2014; Yang et al., 2025). Accordingly, the effects of fermented foods should be evaluated based on microbial function, fermentation, intestinal metabolites, and host responses. Butyrate may support epithelial homeostasis and reduce inflammation, whereas certain secondary bile acids may promote carcinogenesis (Louis et al., 2014; Yang et al., 2025). This framework is more informative than focusing only on the probiotic or antioxidant properties of kombucha.

Kombucha also exhibits direct activity in experimental CRC models. In HCT-116 cells, it altered viability and cell cycle progression and increased apoptosis-related changes in p53, p21, Bax, and Bcl-2; the combination with doxorubicin enhanced several anticancer parameters (Jafari et al., 2022). However, cell culture concentrations, bioavailability, metabolism, microbial interactions, and tissue exposure differ from human physiological conditions. A major gap remains between the extensive evidence on kombucha fermentation, antioxidant and antimicrobial activity, and metabolic effects, and the limited integration with microbial ecology, metabolites, host immune-inflammatory responses, and CRC pathways (Costa et al., 2023; Esatbeyoglu et al., 2024). Product heterogeneity, inadequate strain-level characterization, and a scarcity of human CRC studies prevent claims of therapeutic efficacy. Therefore, this review evaluates kombucha for CRC prevention and adjunctive therapy through the microbiota-metabolite-host axis, integrating fermentation, microbial communities, bioactive compounds, metabolites, gut ecology, oxidative stress, inflammation, immunity, epithelial homeostasis, proliferation, and apoptosis. It distinguishes mechanistic and preclinical plausibility from unverified clinical efficacy.

2. Literature Review and Hypotheses Development

2.1 Colorectal Carcinogenesis: From Molecular Alterations to the Intestinal Microenvironment

Colorectal Cancer (CRC) is a heterogeneous neoplastic disease that develops through complex interactions among genetic, epigenetic, metabolic, immunological, and environmental alterations. The transformation of normal colonic epithelial cells into malignant cells occurs gradually through the accumulation of molecular changes that disrupt the physiological mechanisms controlling proliferation, differentiation, apoptosis, DNA repair, and genomic stability. The principal molecular pathways involved include the activation of Wnt/β-catenin, RAS–RAF–MEK–ERK, and PI3K–AKT pathways, as well as dysregulation of TGF-β and various cell cycle control mechanisms. These changes progressively confer a proliferative and survival advantage to neoplastic cells and support tumor invasion and progression (Hanahan, 2022; Li et al., 2024).

Most CRC cases are sporadic, while a smaller proportion develop in the context of hereditary predisposition, particularly Lynch syndrome and Familial Adenomatous Polyposis (FAP). CRC carcinogenesis can proceed through several routes, both histopathologically and molecularly. The conventional adenoma–carcinoma sequence is characterized by the accumulation of molecular alterations that gradually transform normal mucosa into adenomas and subsequently into invasive

carcinomas. In contrast, the serrated neoplasia pathway is often associated with BRAF/KRAS alterations, CpG Island Methylator Phenotype (CIMP), and, in a subset of tumors, disruption of DNA mismatch repair and Microsatellite Instability (MSI). This heterogeneity indicates that CRC is not a single biological entity but a collection of tumor phenotypes that develop through distinct molecular routes (Li et al., 2024). Advances in the concept of carcinogenesis further indicate that intrinsic changes within tumor cells alone are insufficient to explain the entire CRC process. The tumor microenvironment, immune response, systemic metabolism, dietary exposure, and intestinal microbial community are part of a biological ecosystem that can influence both the initiation and progression of neoplasia. The updated concept of the Hallmarks of Cancer even positions polymorphic microbiomes as one of the characteristics that enable the malignant phenotype to develop, reinforcing the paradigm that tumor–host–microbiome interactions are an important component of cancer biology (Hanahan, 2022).

2.2 Gut Microbiota and Microbial Metabolites in Colorectal Cancer

The colon is one of the most densely populated microbial habitats in the human body. Under physiological conditions, the intestinal microbial community contributes to the metabolism of dietary components, metabolite production, maintenance of epithelial barrier integrity, immune system maturation and mucosal homeostasis. Conversely, changes in microbiota composition or function (dysbiosis) are associated with various gastrointestinal disorders, including CRC. Several studies have shown differences in microbiota profiles among healthy individuals, patients with adenoma, and patients with CRC, although this relationship does not always indicate direct causality and can be influenced by diet, intestinal inflammation, gastrointestinal transit, body mass index, medications, and other clinical factors (Tito et al., 2024; White & Sears, 2024).

The potential mechanism of microbiota in carcinogenesis depends not only on the presence of particular taxa but also on the metabolic function of that community. Intestinal microorganisms can produce or modify various bioactive molecules that interact with the colonic epithelium and the immune system. These products include Short-Chain Fatty Acids (SCFAs), secondary bile acids, tryptophan metabolites, polyamines, sulfur compounds, and various microbial molecules and toxins. Their biological consequences can be either protective or procarcinogenic, depending on the metabolite, concentration, metabolic environment, location, and the host's pathophysiological condition (Louis et al., 2014; Turocy & Crawford, 2025).

Butyrate, for example, is an SCFA produced through the fermentation of fiber by intestinal microorganisms and can contribute to colonic epithelial homeostasis, inflammation regulation, and modulation of gene expression through the inhibition of histone deacetylase. Conversely, changes in bile acid metabolism and increased exposure to certain secondary bile acids can contribute to oxidative stress, epithelial damage, inflammation, and an environment that supports tumorigenesis. Therefore, the relationship between the microbiota and CRC is more appropriately understood as a functional network of interactions among the microbial community, metabolites, and host response, rather than merely a change in the abundance of a single microbial species (Louis et al., 2014; Turocy & Crawford, 2025). A systematic review and meta-analysis of fecal SCFA concentrations further supports this functional perspective by showing an association between SCFA levels and CRC incidence and risk stratification, while also highlighting substantial heterogeneity that limits definitive causal conclusions (Alvandi et al., 2022).

The significance of microbiota in CRC also extends to treatment response. Recent evidence indicates that gut microbiota and its immunomodulatory metabolites potentially influence immune cell activity, intestinal barrier integrity, immune tolerance, and response to immune checkpoint inhibitors. This reinforces the view that the intestinal ecosystem is not only relevant to carcinogenesis but may also influence therapeutic response, a perspective further supported by evidence that the gut microbiota modulates tumor immune surveillance and treatment response through specific microbial taxa and microbiota-based biomarkers relevant to immunotherapy and chemotherapy outcomes (Zhang et al., 2025). Consistent with this, gut microbiota and its metabolites have also been proposed as potential targets for enhancing radioimmunotherapy in CRC by improving tumor immunogenicity and

radiosensitivity (Yuan et al., 2023), while probiotic modulation of the microbiota has more broadly been shown to alter cancer-relevant microbial metabolism across gastrointestinal and extraintestinal tumor sites (Wang et al., 2022). Nonetheless, microbiome–CRC associations must be interpreted cautiously because rigorous control of confounding factors can reduce some microbial associations previously considered specific to CRC (Tito et al., 2024)..

2.3 Kombucha as a Complex Fermented-Food Ecosystem

Kombucha is a fermented beverage generally produced through the fermentation of sugared tea (Camellia sinensis) using a symbiotic community of bacteria and yeast, known as a Symbiotic Culture of Bacteria and Yeast (SCOBY). Based on modern fermented-food concepts, kombucha is more appropriately regarded as a fermentation ecosystem rather than as a tea containing live microorganisms. During fermentation, microbial growth and enzymatic conversion of substrates occur, resulting in substantial changes in the chemical and biological composition of the final product (Marco et al., 2021).

The kombucha microbial community mainly comprises acetic acid bacteria and yeasts, although lactic acid bacteria and other microbial groups are found in certain products. Analyses based on amplicon sequencing and shotgun metagenomics showed that Komagataeibacter can be the dominant bacterial genus, while Zygosaccharomyces is one of the dominant yeasts in a number of kombucha fermentations. The metabolic relationship between bacteria and yeast enables metabolic cross-feeding, which helps maintain the fermentation ecosystem and shapes the metabolic characteristics of the final product (Arıkan et al., 2020).

However, the composition of SCOBY is not universal. Variations in starter source, tea type, sugar concentration, temperature, pH, oxygenation, fermentation duration, geographical conditions, and production method can produce substantial differences in microbial community structure and metabolite profiles. In one kombucha clinical trial, lactic acid bacteria, acetic acid bacteria, and yeasts were found at approximately 10^6 CFU/mL, with Dekkera as the dominant yeast and lactic and acetic acids as the main fermentation products (Mendelson et al., 2023). This heterogeneity is an important consideration when comparing the biological effects of kombucha in different studies.

2.4 From Probiotics to Fermentation-Derived Metabolites

The presence of live microorganisms in kombucha is often the basis for referring to it as a “probiotic” beverage. However, this term should be used with caution. According to the ISAPP consensus, fermented foods are not identical to probiotic foods. A product can only be claimed to contain probiotics if the live microorganisms it contains have been adequately characterized and demonstrated to confer health benefits to the host at an appropriate dose (Hill et al., 2014; Marco et al., 2021). Therefore, the biological effects of kombucha should not be assumed to originate from “probiotics” without the identification of the microorganisms and functional validation at the strain level.

A more comprehensive perspective is to consider the combination of fermenting microorganisms, native tea components, and metabolites that are formed through biotransformation. During fermentation, microbial activity produces organic acids and modifies various bioactive components derived from tea substrates. Kombucha thus provides a complex matrix that may contain polyphenols and their derivatives, acetic, gluconic, and lactic acids, microbial components, and other metabolic products. This composition is highly dependent on the substrate and fermentation conditions; therefore, the biological activity of one kombucha product cannot be generalized to all kombucha products (Coelho et al., 2020; Esatbeyoglu et al., 2024). This concept also needs to be distinguished from that of postbiotics. The ISAPP consensus defines postbiotics as preparations of inanimate microorganisms and/or their components that confer health benefits to the host. Therefore, fermentation metabolites alone do not automatically meet the definition of postbiotics. Nonetheless, metabolites produced during fermentation may still possess independent biological activity and remain important for understanding the health effects of fermented foods (Salminen et al., 2021).

2.5 Kombucha-Gut Microbiota Interaction: A Potential Biological Interface

After consumption, kombucha introduces at least three groups of components that can theoretically interact with the gastrointestinal ecosystem: bioactive compounds derived from tea, metabolites formed during fermentation, and live microorganisms or microbial components present in the final product. These three groups can potentially interact with the resident microbiota and intestinal luminal environment, thereby producing effects different from those of unfermented tea substrates.

Preclinical evidence indicates that kombucha consumption is associated with changes in the gut microbiota composition and metabolic parameters. However, a systematic review of kombucha, gut microbiota, and obesity-related comorbidities showed that most of the evidence still originates from animal models, with substantial heterogeneity in kombucha type, dosage, experimental model, and analyzed parameters (Costa et al., 2023). Consequently, evidence that kombucha consistently remodels the human microbiota is not yet sufficiently robust to serve as the basis for clinical recommendations.

However, evidence from human intervention studies remains limited. A pilot double-blind randomized crossover clinical trial in individuals with type 2 diabetes reported a reduction in fasting blood glucose levels following four weeks of kombucha consumption. Although this study provides preliminary evidence that kombucha components can produce a physiological response in humans, the small number of participants and the non-cancer population mean that the results cannot be extrapolated to the preventive or therapeutic effects of kombucha on CRC (Mendelson et al., 2023).

2.6 Potential Anticancer Mechanisms of Kombucha

The cancer-relevant biological activities of kombucha can be grouped into direct and indirect mechanisms. Direct mechanisms are primarily related to the influence of kombucha components on cancer cell proliferation, the cell cycle, oxidative stress, and apoptosis. In contrast, indirect mechanisms could hypothetically operate through modulation of the intestinal environment, including changes in microbiota activity, luminal metabolism, epithelial barrier integrity, inflammation, and host immune response.

In vitro evidence supports this direct mechanism. In the colorectal cancer cell line HCT-116, kombucha was reported to increase early apoptosis and induce G0/G1 cell cycle arrest, increase the expression of p21, p53, and Bax, and decrease Bcl-2 expression. The combination of kombucha and doxorubicin also increased several anticancer activity parameters in a cell culture system (Jafari et al., 2022). These findings support the possibility that kombucha components can influence proliferation and apoptosis pathways, but their antitumor efficacy has not yet been demonstrated in humans.

In addition, tea polyphenols and their biotransformation products potentially interact with redox and inflammatory pathways. This is relevant because chronic oxidative stress, activation of proinflammatory pathways, altered mucosal immunity, and impaired epithelial integrity are part of the biological environment that supports CRC development. However, in vitro antioxidant effects should not be directly translated into clinical anticancer activity because bioavailability, metabolism, dosage, tissue distribution, and interaction with the microbiota can alter the activity of compounds after consumption.

2.7 The Kombucha Microbiota-Metabolite-Host Axis

Based on this evidence, the potential relationship between kombucha and CRC can be formulated using an integrative framework: the kombucha–microbiota–metabolite–host axis. At the first level, fermentation transforms the tea substrate through the activity of the microbial consortium, producing a matrix containing bioactive components and fermentation-derived metabolites. At the second level, these components can potentially interact with the intestinal microbiota and influence its metabolic activity. At the third level, changes in the microbial metabolome can modulate the luminal environment and interact with the host epithelium and the immune system. The downstream consequences may include changes in intestinal barrier integrity, oxidative stress, inflammation, immune regulation, cellular metabolism, proliferation, and apoptosis.

The biological potential of kombucha for CRC therefore should not be reduced to a single mechanism such as “probiotic activity” or “antioxidant activity.” A more relevant model is a network of interactions: Kombucha fermentation → microbial consortium → bioactive compounds and fermentation-derived metabolites → gut microbiota modulation → microbial metabolome → epithelial and immune responses → CRC-related molecular pathways.

This model also accommodates the possibility that the effects of kombucha may be context-dependent and influenced by product characteristics, dosage, an individual's baseline microbiome, dietary pattern, metabolic status, and disease stage. Given that recent CRC microbiome research shows the substantial influence of confounding factors on microbe–disease associations, validating this mechanism requires a multi-omics approach, microbiome quantification, metabolomics, and controlled intervention studies (Tito et al., 2024).

2.8 Research Gap and Hypothesis Development

Four gaps limit interpretation: the anticancer evidence is predominantly preclinical; kombucha's strain and metabolite composition is heterogeneous; human evidence linking consumption to CRC-relevant microbiota or metabolite changes is scarce; and no adequate trial demonstrates CRC prevention, slower progression, or improved treatment outcomes. Accordingly, this review proposes that the biological potential of kombucha depends on the interactions among tea bioactives, fermenting microorganisms, fermentation metabolites, intestinal microbiota, and host molecular responses, rather than a single component.

H_1: Kombucha-derived bioactive compounds and fermentation metabolites may modulate the composition and metabolic activity of the gut microbiota, thereby promoting an intestinal metabolic environment potentially associated with colorectal homeostasis

H_2: Modulation of the gut microbial metabolome by kombucha may influence epithelial barrier integrity, oxidative stress, inflammatory signaling, and host immune responses relevant to colorectal carcinogenesis

H_3: Bioactive constituents and fermentation-derived metabolites of kombucha may directly or indirectly modulate CRC-related cellular pathways, particularly those involved in proliferation, cell-cycle regulation, and apoptosis

H_4: The potential preventive and adjunctive therapeutic effects of kombucha in CRC are mediated by an integrated microbiota–metabolite–host axis rather than by a single probiotic, antioxidant, or cytotoxic mechanism

3. Research Methodology

3.1 Study Design

This study employed a narrative literature review with an analytical and mechanistic approach to critically synthesize the current evidence regarding the potential role of kombucha in preventing and treating Colorectal Cancer (CRC). Rather than focusing exclusively on the direct cytotoxic activity of kombucha, this review was structured around the microbiota–metabolite–host axis, integrating evidence on kombucha fermentation, microbial composition, fermentation-derived metabolites, gut microbiota modulation, host inflammatory and immune responses, and molecular pathways associated with colorectal carcinogenesis. A narrative review design was selected because the available literature is heterogeneous in terms of experimental models, kombucha substrates, fermentation conditions, microbial composition, metabolites investigated, biological outcomes, and study methodologies. The available evidence includes in vitro, in vivo, in silico, microbiological, metabolomic, and limited human studies, precluding direct quantitative pooling while supporting critical mechanistic synthesis.

3.2 Literature Search Strategy

A structured literature search was conducted using PubMed/MEDLINE, ScienceDirect, and Google Scholar to identify relevant peer-reviewed publications related to kombucha, Colorectal Cancer

(CRC), microbiota, microbial metabolites, and host responses. The primary search period included studies published from January 2015 to December 2025, while seminal publications prior to 2015 were retained if they provided essential conceptual foundations regarding probiotics, fermented foods, microbial metabolites, colorectal carcinogenesis, and microbiota–host interactions. The search strategy incorporated both controlled vocabulary AND and OR free-text terms, where applicable, using the Boolean operators AND and OR. The main search combination included ("kombucha" OR "fermented tea" OR "SCOBY") AND ("colorectal cancer" OR "colon cancer" OR "colorectal carcinoma"), followed by additional searches using combinations of ("kombucha" OR "fermented tea") AND ("gut microbiota" OR "gut microbiome" OR "intestinal microbiota"); ("kombucha" OR "fermented tea") AND ("metabolites" OR "organic acids" OR "polyphenols" OR "bioactive compounds"); ("gut microbiota" OR "microbiome") AND ("microbial metabolites" OR "short-chain fatty acids" OR "bile acids") AND ("colorectal cancer"); and ("kombucha" OR "fermented tea") AND ("antioxidant" OR "inflammation" OR "immune response" OR "apoptosis" OR "cell proliferation" OR "anticancer"). This comprehensive search approach aimed to capture both direct evidence from studies evaluating the effects of kombucha in CRC-related models and indirect mechanistic evidence explaining the potential interactions among fermented-food-derived compounds, microbial metabolism, gut microbiota modulation, host responses, and molecular pathways associated with colorectal carcinogenesis.

3.3 Eligibility Criteria

Studies were considered eligible if they fulfilled one or more of the following criteria: First, they investigated kombucha or fermented tea in relation to CRC or cancer-related biological processes. Second, the microbial composition, bioactive compounds, and fermentation-derived metabolites of kombucha were characterized. Third, we evaluated the influence of kombucha on the gut microbiota and gastrointestinal biological responses. Fourth, we investigated microbial metabolites and microbiota-related mechanisms relevant to colorectal carcinogenesis. Fifth, mechanistic evidence concerning oxidative stress, inflammation, immune regulation, epithelial homeostasis, proliferation, cell cycle regulation, or apoptosis relevant to the proposed microbiota–metabolite–host axis should be provided.

Eligible evidence included peer-reviewed original research employing in vitro, in vivo, in silico, microbiological, molecular, metabolomic, or human study designs, as well as high-quality systematic reviews, consensus statements, and authoritative narrative reviews used to establish conceptual and mechanistic foundations of the research topic. Studies were excluded if they were unrelated to kombucha, fermented-food biology, gut microbiota, microbial metabolites, or CRC; lacked sufficient methodological information; consisted solely of abstracts, conference proceedings, editorials, commercial webpages, or non-scientific sources; duplicated previously identified publications; or presented claims that could not be traced to an identifiable primary or authoritative scientific source.

3.4 Study Selection and Data Extraction

The retrieved literature was screened sequentially based on the title, abstract, and full-text relevance. Duplicate records and studies that did not meet the predefined eligibility criteria were excluded from the review. Because this study was designed as an analytical narrative review rather than a systematic review or meta-analysis, study selection emphasized relevance, methodological quality, mechanistic contribution, and coherence with the conceptual framework rather than statistical comparability among studies.

Relevant information was extracted into a structured evidence matrix comprising the author and year, study design, experimental model or population, type and substrate of kombucha, fermentation characteristics when available, microbial components, major bioactive compounds or metabolites, biological targets, CRC-related outcomes, principal findings, proposed mechanisms, and major limitations. Particular attention was given to evidence related to the interconnected aspects of kombucha microbial ecology and fermentation processes, fermentation-derived bioactive compounds and metabolites, modulation of gut microbiota and microbial metabolites, and host molecular responses associated with colorectal cancer development and progression.

3.5 Evidence Synthesis and Mechanistic Framework

The extracted evidence was qualitatively synthesized using a mechanism-oriented thematic approach. The findings were organized into several interconnected mechanistic domains, including kombucha microbial composition and fermentation ecology, fermentation-derived polyphenols, organic acids, and bioactive metabolites; antioxidant and redox-regulatory activities; modulation of gut microbiota and microbial metabolism; inflammatory and immune regulation; and regulation of cancer-related cellular processes, such as proliferation, cell cycle progression, and apoptosis. These domains were subsequently integrated into the proposed kombucha–microbiota–metabolite–host axis, which describes a conceptual pathway beginning with kombucha fermentation and microbial biotransformation, followed by the generation of bioactive compounds and metabolites, interaction with intestinal microbiota, modulation of microbial metabolites, and subsequent effects on epithelial, metabolic, inflammatory, and immune responses associated with CRC-related pathways.

Evidence interpretation was performed according to the translational relevance level. Findings from CRC cell line studies were classified as in vitro mechanistic evidence, whereas results derived from animal models were considered preclinical evidence. Computational analyses were categorized as hypothesis-generating in silico evidence, whereas human intervention studies were evaluated separately as clinical evidence. This hierarchical framework was applied to ensure appropriate interpretation of the findings and to prevent direct extrapolation of cytotoxic, molecular, or animal-based observations into claims regarding clinical efficacy.

3.6 Critical Appraisal and Interpretation

The interpretation of the evidence considered several sources of heterogeneity, including differences in tea substrates, SCOBY composition, fermentation duration, pH, microbial abundance, metabolite profiles, kombucha concentrations, experimental models, and outcome measurements. Particular caution was applied to studies reporting “probiotic” effects because the presence of viable microorganisms in fermented foods does not, by itself, establish probiotic status unless the microorganisms are adequately characterized and associated with the demonstrated health benefits.

Similarly, the anticancer activity observed in cell cultures or animal models was interpreted as evidence of biological plausibility rather than proof of therapeutic efficacy. Therefore, the overall synthesis distinguished between direct experimental evidence, indirect mechanistic evidence, and proposed biological pathways, allowing the strengths and limitations of the evidence supporting the kombucha–microbiota–metabolite–host axis in CRC to be critically evaluated, a shown in the Table 1.

Table 1. Synthesis of Experimental, Preclinical, Clinical, and Mechanistic Evidence Supporting the Kombucha–Microbiota–Metabolite–Host Axis in Colorectal Cancer

Study	Design/Model	Kombucha/Intervention	Key Findings
Jafari et al. (2022)	In vitro; human colorectal cancer cell line HCT-116	Green tea kombucha, green tea extract, doxorubicin, and combined treatment	Kombucha increased early apoptosis and caused cell cycle arrest in the G0/G1 phase. Kombucha treatment also increased the expression of p21, p53, and Bax, while decreasing Bcl-2 expression, indicating the activation of pro-apoptotic mechanisms. The combination of kombucha and doxorubicin increased several anticancer response parameters compared to either treatment alone.

Study	Design/Model	Kombucha/Intervention	Key Findings
Kaewkod et al. (2019)	Experimental in vitro	Kombucha prepared from green tea, oolong tea, and black tea	The substrate type and fermentation process influenced the physicochemical characteristics, organic-acid profiles, antioxidant activity, antimicrobial activity, and cytotoxicity. Green tea and black tea kombucha exhibited higher cytotoxicity toward cancer cells than toward normal cells under experimental conditions, indicating potential anticancer activity influenced by the fermentation composition.
Sinaga et al. (2024)	Experimental in vivo and in silico approach	Pirdot kombucha (Saurauia vulcani)	Pirdot kombucha ameliorated histopathological changes and reduced IL-1β levels in an experimental CRC-related model. Network pharmacology analysis and molecular approaches indicated possible interactions between pirdot bioactive compounds and molecular targets associated with CRC, supporting potential anti-inflammatory and anticancer mechanisms.
Costa et al. (2023)	Systematic review of preclinical evidence	Kombucha	Available evidence indicates that kombucha consumption may modulate the gut microbiota composition and metabolic parameters. However, substantial heterogeneity exists in experimental models, kombucha type and composition, dosage, and analyzed outcomes; therefore, generalization of the biological effects remains limited.
Mendelson et al. (2023)	Randomized controlled pilot crossover trial; humans with type 2 diabetes	Kombucha consumption for 4 weeks	Kombucha consumption was associated with a reduction in fasting blood glucose levels in a small pilot study. This finding provides preliminary evidence of the metabolic effect of kombucha in humans; however, the study was not conducted in patients with CRC and therefore cannot be used as direct evidence of anticancer efficacy.

Study	Design/Model	Kombucha/Intervention	Key Findings
White & Sears (2024)	Mechanistic review	Microbiota associated with CRC	CRC is associated with complex changes in the ecology and function of intestinal microbiota. These changes can potentially influence inflammation, immune response, metabolism, mucosal integrity, and tumor biology, supporting the role of the microbiota as an important component of the CRC microenvironment.
Turocy & Crawford (2025)	Mechanistic review	Bacterial metabolites in gastrointestinal cancer	Small molecules produced or modified by the microbiota can influence epithelial biology, immune responses, metabolism, and gastrointestinal carcinogenesis. These findings reinforce the concept that the metabolic function of the microbiota, in addition to its taxonomic composition, plays a role in microbiota–host interactions in cancer.
Tito et al. (2024)	Human CRC microbiome analysis	Gut microbiome	The study showed that intestinal transit time, intestinal inflammation, body mass index (BMI), and other factors can act as confounders in the relationship between the microbiome and CRC. These findings emphasize the importance of controlling confounders before concluding a causal relationship between microbiota alterations and CRC development.

4. Results and Discussions

4.1 Current Therapeutic Landscape of Colorectal Cancer and the Rationale for Complementary Approaches

Colorectal Cancer (CRC) management is a multidisciplinary approach determined by tumor location, disease stage, histopathological characteristics, patient performance status, comorbidities, and tumor molecular profile. The main treatment modalities include surgery, chemotherapy, radiotherapy (particularly for rectal cancer), targeted therapy, and immunotherapy for specific molecular subgroups. The development of precision oncology increasingly places molecular biomarkers as an important component in treatment selection, particularly the mismatch repair/microsatellite instability (dMMR/MSI-H) status, RAS, BRAF, and other molecular targets. CRC is currently understood as a heterogeneous biological disease requiring individualized treatment strategies rather than a single entity treated uniformly.

Although standard therapy has improved clinical outcomes, treatment toxicity, drug resistance, recurrence, response heterogeneity, and metastatic disease progression remain challenges. This condition has driven the exploration of complementary strategies based on diet and microbiome modulation. However, such approaches must be positioned as complementary or adjunctive strategies, not as replacements for surgery, chemotherapy, radiotherapy, targeted therapy, or immunotherapy, which already have established clinical evidence. Broader public receptivity toward such novel

complementary interventions, whether pharmaceutical or dietary, ultimately depends on clear, evidence-based health communication, as illustrated by studies on public hesitancy toward other evidence-based health interventions (Wee et al., 2025).

In this context, kombucha is of interest not only because of its antioxidant activity but also because it is a complex fermentation matrix containing tea components, fermenting microorganisms, polyphenols and their biotransformation products, and various organic acids and fermentation metabolites. This combination provides a biological basis for evaluating kombucha through the interaction among fermentation-derived metabolites, gut microbiota, and host responses, particularly because the intestinal microbiota interacts directly with the colonic environment and potentially influences the development and progression of CRC (White & Sears, 2024).

4.2 Direct Antiproliferative and Pro-Apoptotic Effects of Kombucha

Direct evidence of the anti-CRC activity against CRC still mainly originates from in vitro studies. Kaewkod et al. (2019) evaluated kombucha fermented from green, oolong, and black tea and showed that the substrate type and fermentation duration influence the physicochemical characteristics and biological activity of the product. Green tea kombucha showed high antioxidant activity, whereas black tea kombucha had different total acidity and organic acid profiles. The study also demonstrated cytotoxic activity against Caco-2 colorectal cancer cells under experimental conditions. These findings are important because they demonstrate that the fermentation substrate and kombucha metabolome are potential determinants of biological activity. Thus, the term “kombucha” cannot be considered a single, identical biological intervention. Differences in tea type, substrate concentration, microbial community structure, fermentation duration, temperature, pH, and oxygenation can potentially produce different metabolite profiles and ultimately different biological responses. This heterogeneity is one of the main challenges in translating the evidence on kombucha into clinical applications.

More specific mechanistic evidence was obtained from HCT-116 CRC cells. Jafari et al. (2022) showed that green tea kombucha treatment was associated with increased early apoptosis and cell cycle arrest at the G0/G1 phase. At the molecular level, this response was accompanied by increased expression of p53, p21, and Bax and decreased expression of Bcl-2, resulting in a shift in the molecular balance toward a pro-apoptotic state. The combination of kombucha and doxorubicin also increased several anticancer response parameters in the cell culture system. These findings provide proof-of-concept evidence that kombucha components can influence two fundamental processes in cancer biology: the control of proliferation and apoptosis. However, the term “synergistic” should be used cautiously when a study does not perform a formal drug interaction/synergy analysis, such as a combination index. The improved response observed with combination therapy is more appropriately interpreted as an enhanced combined effect until a genuine pharmacological interaction is demonstrated. More importantly, the kombucha concentration that produces cytotoxic activity in cell culture cannot be directly equated with colonic tissue exposure after oral consumption. Digestion, absorption, metabolism, biotransformation by the microbiota, bioavailability, and metabolite distribution can substantially alter the in vivo biological exposure. Therefore, although the in vitro findings support biological plausibility, the therapeutic efficacy of kombucha in human CRC has not yet been demonstrated..

4.3 Fermentation-Derived Metabolites as a Mechanistic Bridge

The literature synthesis indicates that the biological activity of kombucha does not originate from a single compound. Fermentation produces a complex biochemical system through the interactions among tea substrate, yeast, acetic acid bacteria, and, in some products, other microbial groups. This process generates organic acids and alters the structures and availability of various phenolic compounds. Fermentation can therefore be regarded as a process of microbial biotransformation that converts the chemical composition of tea into a fermentation-derived metabolome with characteristics that are distinct from those of the starting material. Kaewkod et al. (2019), for example, showed differences in organic acid profiles among kombucha derived from green, oolong, and black tea. This variation provides a biological explanation for the differences in antioxidant, antimicrobial, and

cytotoxic activities across products. This suggests that the activity of kombucha is likely a consequence of the interaction among substrate, microorganisms, and metabolites, rather than merely an effect of live microorganisms or tea polyphenols in isolation.

This concept is highly relevant to CRC because metabolites are the principal mediators of microbiota–host communication. Recent literature indicates that SCFAs, particularly butyrate, are associated with intestinal barrier integrity, inflammation modulation, and metabolic regulation, whereas other metabolite changes can produce different or even pro-carcinogenic effects. Therefore, the effect of an intervention on cancer cannot be inferred solely from an increase or decrease in one bacterial group; the metabolic function of the microbial community is a variable more closely linked to the host's biological response.

4.4 Gut Microbiota as an Interface Between Kombucha and Colorectal Carcinogenesis

The potential role of kombucha in CRC becomes more compelling when placed in the context of intestinal microbiota ecology. Intestinal microorganisms are in direct contact with the colon and can influence inflammation, immune response, metabolism, DNA damage, and tumor microenvironment. White and Sears (2024) showed that CRC development is associated with complex changes in the structure and function of the microbial community, positioning the microbiota as a biological component that can contribute to both initiation and progression of CRC.

Nonetheless, the term “dysbiosis causes CRC” should be avoided in the future. A large-scale human analysis by Tito et al. (2024) showed that intestinal transit time, intestinal inflammation, and BMI are important covariates that can influence the relationship between the microbiome and CRC. After controlling for these factors, several microbial associations previously considered characteristic of CRC became weaker. This finding has direct implications for the interpretation of the results of kombucha studies. Changes in microbiota composition following kombucha consumption cannot be regarded as an anticancer mechanism unless accompanied by functional evidence, such as changes in metabolites, immune response, epithelial integrity, or cancer-related signaling. Future research therefore needs to move from the approach of “which bacteria are present?” toward “what are they doing, which metabolites are produced, and how does the host respond?”

4.5 Inflammation and Host Response: Evidence from Pirdot Kombucha

The host-response dimension is supported by the study of Sinaga et al. (2024), who used pirdot-based kombucha (Saurauia vulcani) in a benzo[a]pyrene-induced rat model and integrated an in vivo approach with network pharmacology and computational analyses. Administration of pirdot kombucha reportedly reduces colonic histoarchitectural damage and suppresses IL-1β levels, a proinflammatory mediator relevant to the proinflammatory environment of carcinogenesis. Network pharmacology analysis identified several targets associated with CRC mechanisms, including CTNNB1, AKT1, CASP3, TP53, EGFR, MTOR, STAT3, PTEN, and FOXO3. In addition, epitope similarity analysis revealed sequence relationships between CRC-related epitopes and kombucha microorganisms, such as Lactiplantibacillus plantarum and Saccharomyces cerevisiae.

These findings are of interest because they connect metabolite/bioactive component → inflammation → molecular targets → host response. However, their interpretation must remain proportional. Network pharmacology, molecular docking, and epitope similarity constitute hypothesis-generating evidence, not proof that this interaction occurs physiologically in humans. In addition, pirdot is not Camellia sinensis; therefore, the biological effects of pirdot kombucha may originate from the bioactive components of S. vulcani, fermentation, microorganisms, or an interaction among the three. Therefore, these findings cannot be directly generalized to conventional tea kombucha..

4.6 Integrating the Evidence: The Kombucha–Microbiota–Metabolite–Host Axis

When these three layers of evidence are integrated, a mechanism emerges that is broader than the antioxidant or cytotoxic activity of kombucha alone. Kaewkod et al. (2019) provided evidence that substrate and fermentation determine the metabolites and biological activity. Jafari et al. (2022) provided evidence that kombucha influences cell cycle regulation and apoptosis in CRC cells. Sinaga

et al. (2024) extended this mechanism to inflammation and tissue response in vivo. The CRC microbiome literature provides a conceptual link between fermented products, metabolites, and host responses. Based on this synthesis, the mechanistic model proposed in this review is as follows: kombucha fermentation → microbial consortium → biotransformation of tea bioactives → fermentation-derived metabolites → interaction with resident gut microbiota → altered microbial metabolome → epithelial, redox, inflammatory, metabolic, and immune responses → modulation of CRC-related cellular pathways.

This model constitutes the core of the kombucha–microbiota–metabolite–host interaction axis. On the hypothesized protective side, changes in the metabolic environment may support epithelial barrier integrity and inflammation regulation, whereas certain bioactive components may influence oxidative stress, proliferation, cell cycle control, and apoptosis. Recent CRC literature supports the importance of microbiota-derived metabolites as mediators between the microbial community and host physiology, including in the context of disease modulation and precision therapy strategies. However, this model has not yet been proven to be a causal pathway. In particular, the complete evidence chain of kombucha consumption → changes in the human microbiome → changes in the metabolome → changes in CRC biomarkers → improved clinical outcomes has not been demonstrated in clinical trials. This is the essential difference between mechanistic plausibility and clinical efficacy..

4.7 Concordance With the Proposed Hypotheses

The synthesized results provide varying strengths of support for the hypotheses developed earlier. H1, concerning the capacity of kombucha components and metabolites to modulate the microbiota and intestinal metabolic environment, is supported mainly by preclinical evidence and fermented food literature; however, evidence from human CRC remains inadequate. H2, concerning the modulation of epithelial integrity, oxidative stress, inflammation, and immune response, receives indirect support from the microbiota–metabolite literature and *in vivo* evidence of altered IL-1β in the Pirdot Kombucha model.

The most direct support was found for *H3*, namely the potential of kombucha components to influence proliferation, the cell cycle, and apoptosis, based on the HCT-116 and Caco-2 studies. However, this evidence remains at the *in vitro* stage. Overall, the findings are most consistent with *H4*, namely that the biological potential of kombucha is more rationally explained through an integrated mechanism than through a single "probiotic," antioxidant, or cytotoxic effect. Nonetheless, H4 remains an integrative mechanistic proposition rather than a clinically validated mechanism.

4.8 Translational Gaps and Future Research

The greatest gap in the literature is the imbalance between mechanistic and clinical evidence. Studies directly testing kombucha against CRC remain limited and are dominated by cell culture and animal models. In addition, variations in tea or plant type, SCOBY composition, fermentation duration, sugar concentration, pH, live microorganism count, and metabolite profile limit reproducibility and generalizability across studies.

Future research should use standardized kombucha characterized by metagenomics, metabolomics, and targeted chemical profiling. Preclinical trials should integrate microbiome profiling with SCFAs, bile acids, tryptophan metabolites, inflammatory biomarkers, epithelial integrity, and tumor molecular pathways. In human studies, confounders such as diet, BMI, antibiotic and other medication use, intestinal inflammation, and intestinal transit time must be controlled, because these factors can produce microbiome changes that are erroneously interpreted as an effect of the disease or intervention.

The next stage requires controlled clinical trials that first focus on safety, tolerability, pharmacometabolomics, microbiome response, and biomarker modulation before evaluating the oncological endpoints. Such designs also need to stratify patients according to CRC molecular characteristics and standard therapy received. Effective translation of such trials into practice and public acceptance of kombucha or similar fermented-food interventions as legitimate complementary

strategies will also depend on how clearly their evidentiary status is communicated to patients and the public, an issue also underscored by research on public perception and understanding of other health-related products (Agao et al., 2025). Based on the currently available evidence, kombucha is therefore more appropriately positioned as a candidate functional fermented-food intervention for mechanistic and translational investigation, rather than as a proven CRC therapy

4.9 Overall Interpretation

Overall, this review indicates that kombucha has biological plausibility for influencing processes relevant to colorectal carcinogenesis through several interconnected mechanisms. In vitro evidence supports the effects on proliferation, the cell cycle, and apoptosis; early in vivo evidence suggests possible modulation of inflammation and tissue integrity; and the microbiome and metabolite literature provides a biological foundation linking fermentation with intestinal and systemic responses.

Accordingly, the main contribution of this review is not to conclude that kombucha is a proven therapy for colorectal cancer, but rather to propose that its potential effects can be understood through the microbiota–metabolite–host axis. This framework shifts the perspective from the simple model "kombucha → antioxidant → anticancer" toward the multidimensional model "fermentation → microbial ecology → metabolite biotransformation → gut microbiota → host response → CRC-associated signaling." This model simultaneously provides a testable biological hypothesis for future multi-omics, preclinical, and clinical studies.

5. Conclusions

5.1 Conclusion

Based on the synthesis of available evidence, kombucha shows biological potential as a functional fermented beverage that may influence several mechanisms relevant to the prevention and progression of Colorectal Cancer (CRC). Experimental evidence indicates that kombucha and its fermentation-derived bioactive components can influence cell proliferation, cell cycle regulation, and apoptosis, including by modulating the p53/p21 pathway and the balance between the pro-apoptotic protein Bax and the anti-apoptotic protein Bcl-2. Preclinical evidence also suggests the possible involvement of anti-inflammatory mechanisms and modulation of tissue responses. However, these findings mainly originate from in vitro research, animal models, and in silico approaches and therefore cannot yet be interpreted as evidence of the therapeutic efficacy of kombucha in CRC patients.

Conceptually, the potential relevance of kombucha to CRC appears to be more appropriately understood through the kombucha–microbiota–metabolite–host axis than through a single mechanism, such as antioxidant activity or a "probiotic" effect. Fermentation results in complex interactions among the microbial community, bioactive tea components, and biotransformation metabolites. After consumption, these components can potentially interact with the intestinal microbiota and influence the microbial metabolome, which in turn can interact with the colonic epithelium, redox environment, inflammatory and immune responses, and molecular pathways involved in carcinogenesis. This framework provides biological plausibility linking fermented foods with intestinal homeostasis and CRC biology; however, its causal relationship requires experimental and clinical validation.

5.2 Research Limitations

The most important evidence gap lies in the heterogeneity of kombucha composition and the limited number of human studies. Differences in substrate, SCOBY community structure, fermentation conditions and duration, live microorganism content, and metabolite profile can result in different biological activities across products. This review is further limited by its narrative rather than systematic design, which, while suited to synthesizing mechanistically heterogeneous evidence, does not permit formal quantitative pooling or a standardized risk of bias assessment of the included studies. In addition, most of the evidence synthesized in this review originates from in vitro and animal models; therefore, extrapolation of these mechanistic findings to human colorectal carcinogenesis should be undertaken with caution.

5.3 Suggestions and Directions for Future Study

Future research should employ standardized kombucha products that are comprehensively characterized using metagenomic, metabolomic, and targeted chemical-profiling approaches, accompanied by an evaluation of changes in gut microbiota, microbial metabolites, inflammatory biomarkers, intestinal barrier integrity, and CRC-related molecular pathways. Controlled clinical trials in humans are subsequently needed to determine the safety, tolerability, dosage, consumption patterns, long-term effects, interactions with anticancer therapy, and microbiome and metabolome responses before efficacy on oncological outcomes can be evaluated. Potential interactions between kombucha and chemotherapy, targeted therapy, or immunotherapy warrant particular attention to ensure that the hypothesized benefits are not accompanied by unintended interaction risks.

Based on the currently available evidence, kombucha cannot yet be recommended as a therapy for or substitute for standard colorectal cancer treatment. Kombucha is more appropriately positioned as a candidate functional fermented food intervention for further mechanistic and translational research, with the microbiota–metabolite–host axis serving as a promising framework for explaining the potential relationship among fermentation, microbial metabolism, host response, and colorectal carcinogenesis. Validation through multi-omics research, standardized preclinical models, and high-quality clinical trials will determine whether this biological potential can be ultimately translated into a safe and effective complementary strategy for CRC prevention or supportive care.

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Author Contributions

KNB contributed to the conceptualization, study design, literature search strategy, evidence synthesis, and drafting of the manuscript. YNP contributed to the literature analysis, data interpretation, and development of the mechanistic framework. MA contributed to the manuscript preparation, critical review of the scientific content, and refinement of the discussion. AY contributed to the methodological supervision, validation of the review approach, and critical revision of the manuscript. IDR contributed to the literature evaluation, manuscript editing, and final review. All authors contributed to the discussion of the findings, approved the final version of the manuscript, and agreed to be held accountable for all aspects of the work.

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