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AN ANALYSIS OF RANDOMIZED CONTROL TRIALS OF MICROBIOME ALTERATION AND DIET IN GASTRIC CANCER IN HUMANS-A SYSTEMATIC REVIEW

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ABSTRACT

Gastric cancer (GC) remains a leading cause of cancer mortality. Growing evidence links diet and the gut microbiome to GC risk and outcomes. Systematic search of PubMed, EMBASE, Cochrane CENTRAL, and Web of Science (January 2000–June 2025) following PRISMA 2020. RCTs in adults with GC or precancerous lesions evaluating *H. pylori* eradication, vitamins/garlic, fiber, probiotics, or synbiotics were included. Quality was appraised with the Jadad tool. Five RCTs (from 410 records) show that 2-week *H. pylori* eradication lowers gastric cancer incidence and mortality, with vitamin C/E/selenium and aged garlic adding mortality benefits especially in nutritionally vulnerable or non-drinkers. Perioperative fiber-enriched nutrition plus probiotics reduced diarrhoea and length of stay; multistrain probiotics improved inflammatory, immune, and nutritional markers and restored beneficial taxa. In precancerous lesions, a 12-week high-fiber diet increased SCFA-producing bacteria and reduced inflammation. Overall quality was moderate to high. Microbiome and dietary interventions—especially early *H. pylori* eradication, perioperative fiber/probiotics, and long-term micronutrient/garlic supplementation—offer clinically meaningful benefits across GC prevention and care. Effects appear modified by lifestyle behaviors (smoking, alcohol). Future multicentre RCTs should standardize microbiome endpoints, stratify by baseline nutrition and risk behaviors, and test individualized, microbiome-guided strategies. Clinical integration appears feasible and low risk.

Introduction:

Cancer occurs when cells grow and proliferate uncontrollably, resulting in tumours [1]. Gastric cancer is a heterogeneous malignant disease with genetic and environmental risk factors. Although there has been a pronounced decrease in incidence and mortality during the last few decades, stomach cancer remains the fourth most common cause of cancer related mortality worldwide [2]. Helicobacter pylori infection is extremely common, affecting almost half the global population [3]. A high-fat diet (HFD) is the primary source of obesity, which is a risk factor for gastrointestinal cancer. It has a high fatty acid but low fibre, vitamin, and mineral content [4]. Obesity is a global health condition that has become prominent in recent years and leads to the occurrence of various chronic diseases [5].

The global incidence of gastric cancer, a common and lethal neoplasm, has decreased over the past three decades. Risk factors include age, Helicobacter pylori infection, hereditary disorders, and eating habits. Helicobacter pylori infection is the most significant risk factor for gastric cancer development, as it is a precursor to the intestinal form of non-cardia gastric cancer, which accounts for most cases. This type of cancer progresses from atrophic gastritis to gastric cancer [6-9]. The challenge of cultivating commensal microorganisms that live in the stomach contributed to the limitations of early studies on the gastric microbiota. Because of this, scientists traditionally thought there was a limit to the number of microorganisms that could survive in the stomach [10]. However, breakthroughs in PCR methods and metagenomics have revealed that the stomach has a strong microbiota [11].

As of now, gastric cancer has been treated with surgery, radiation therapy, chemotherapy, gene therapy, and immunotherapy. The most common surgical procedure for individuals with gastric cancer is gastrectomy [12,13,14]. However, only a small amount of food may be permitted into the small intestine at a time due to the whole or partial removal of the stomach, which results in postoperative symptoms such as dysphagia, heartburn, and nutritional issues [15,16,17]. With the emergence of the metagenome and macro transcriptome in recent years, research into gut bacteria has reached a new high. [18,19]

These advancements in technology are now starting to enhance research into the connection between the connection between gastric microbiota and stomach cancer. Comparison and assessment of the research results are necessary to identify probable future research directions within this innovative area. Intestinal cancer is also associated with pro-inflammatory gene mutations [20]. Epidemiologic studies are strong evidence of the association of Helicobacter pylori infection with gastric cancer development and the progression of precancerous gastric lesions. They also demonstrate that diets high in vitamins and garlic may prevent gastric cancer in high-risk individuals who do not consume enough vitamins [21,22,23].

Materials and methods

The literature search was performed using the following databases: PubMed, EMBASE, Cochrane CENTRAL, and Web of Science. The search was done for articles published from January 2000 to June 2025. Search terms were used in combinations of the following keywords and MeSH terms: "gastric cancer", "stomach neoplasm", "microbiome", "gut microbiota", "diet", "nutrition", "probiotics", "prebiotics", "synbiotics", "fecal microbiota transplantation", and "randomized controlled trial". This systematic review aligned with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency and methodological rigor [Figure1]. The included randomized trials' methodological quality and risk of bias

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were assessed using the JADAD bias tool [24].

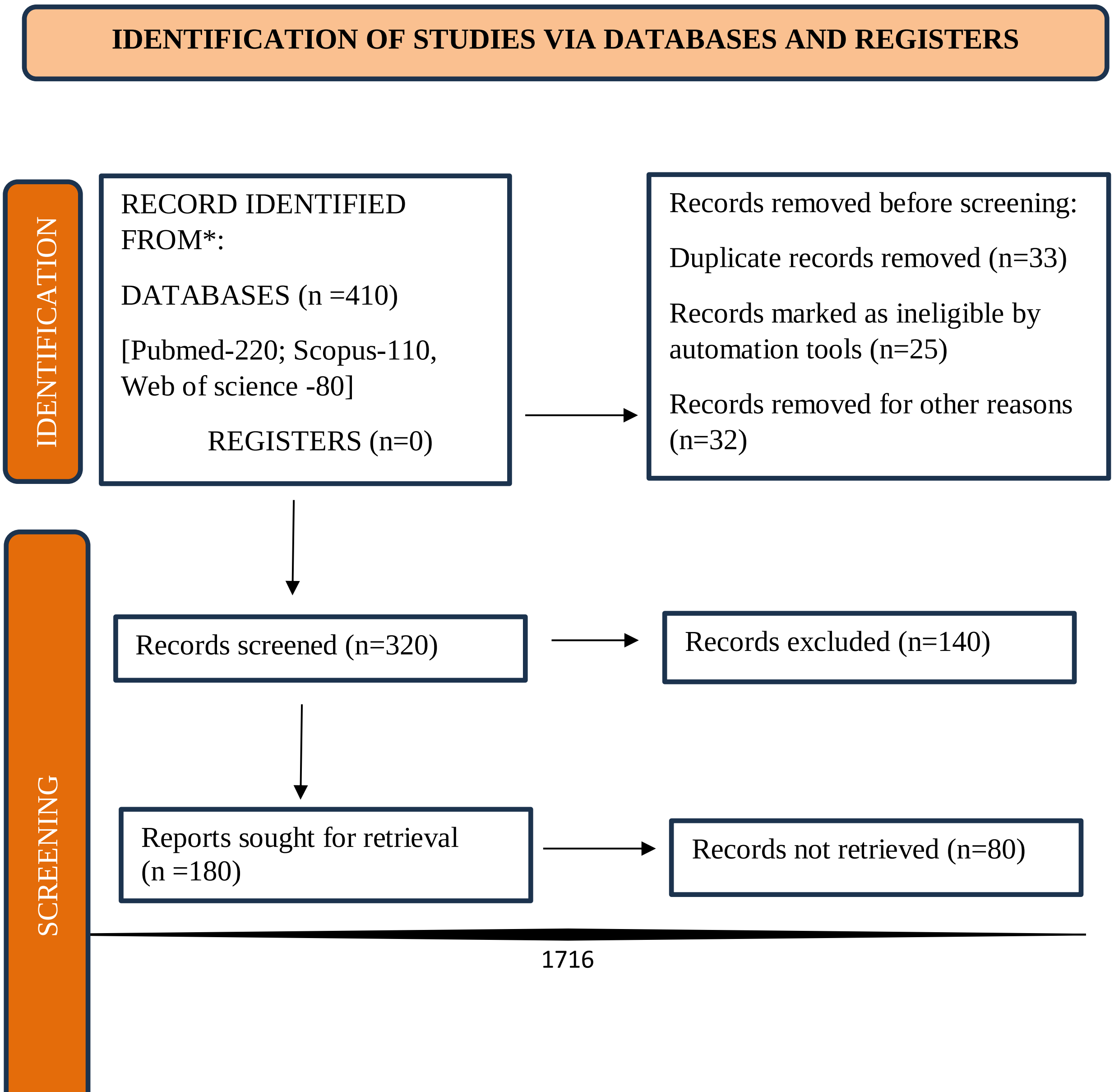
Inclusion Criteria

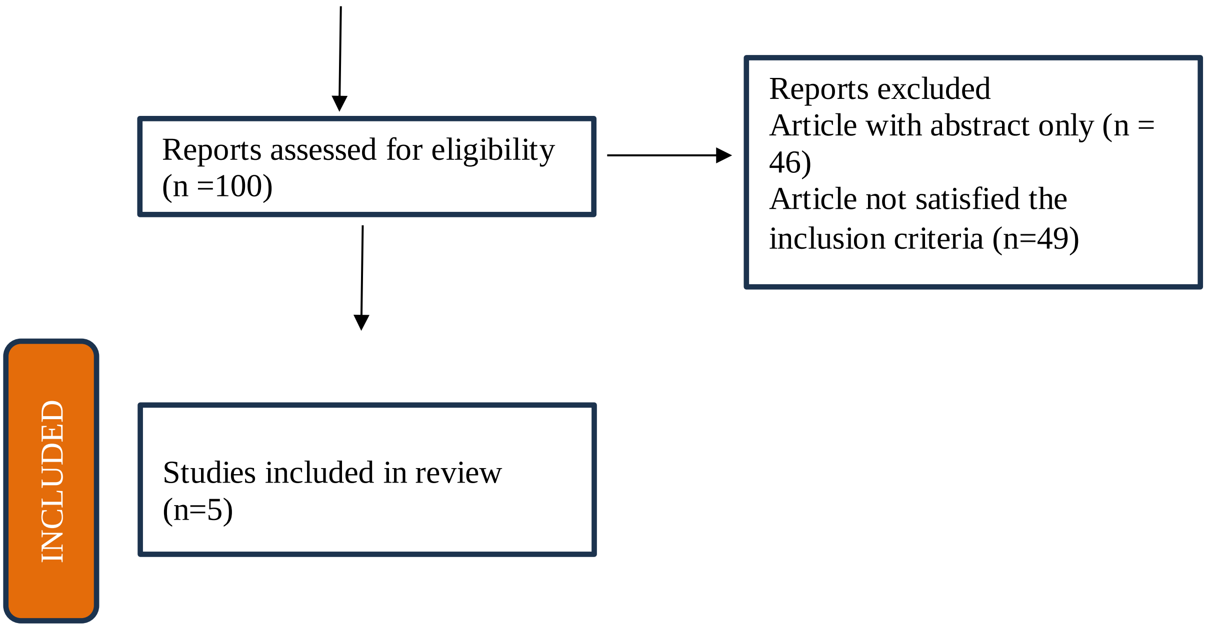
- Randomized Controlled Trials (RCTs) in peer-reviewed publications.
- Involving human subjects 18 years and above who had gastric cancer.
- Printed in English from January 2000 to June 2025.

Exclusion Criteria

- Non-human (animal or in vitro) studies.
- Study designs other than RCTs include observational studies, case reports, case series, reviews, editorials, or conference abstracts.
- Articles not specifically involving gastric cancer or not focused on microbiome/diet-related interventions.
- Studies with insufficient data, inaccessible full texts, or unclear outcome reporting.
- A study combining multiple interventions (such as surgery, chemotherapy, and diet) in which microbiome or dietary factors were not evaluated separately.

Figure 1: PRISMA 2020 flow diagram for newly conducted systematic reviews that solely involved database and registration searches.





Results:

This research resulted in 180 articles, of which 100 were full-text articles having accessibility and were eligible for review. Ultimately, 5 articles were chosen for inclusion in this systematic review. **Table 1** shows the Summary of Randomized Trials Evaluating Dietary and Probiotic Interventions in Gastric Cancer. **Table 2** shows Microbiome Alteration and Dietary Impact on Gastrointestinal Cancer Risk. The **Table 3** shows bias assessment which were evaluated using the Jadad scale, which assesses methodological quality based on randomization, blinding, and reporting of withdrawals. All studies reported randomization, with four detailing appropriate methods. Double-blinding was clearly described in Li et al. (2019) and Guo et al. (2020), and partially in Zheng et al. (2019), while Zhao et al. (2017) and Zhou et al. (2021) lacked blinding. All studies adequately reported dropouts. Li et al. and Guo et al. received the highest score (5/5), indicating low risk of bias. Zheng et al. scored 4, and both Zhao et al. and Zhou et al. scored 3, suggesting moderate quality with room for improvement in blinding procedures. Overall, the trials demonstrate acceptable to high methodological quality.

Table 1: Summary of Randomized Trials Evaluating Dietary and Probiotic Interventions in Gastric Cancer:

	Author Name	**Study Design**	**Sample Size**	**Intervention**	**Duration/ Comparison**	**Diseases stages**

1.	Li et al. (2019) [25]	Randomized, factorial trial	Total: 3365 (Vitamin group: 1677 vs Placebo: 1688; Garlic group: 1678 vs Placebo: 1687)	H. pylori eradication therapy: Amoxicillin 1 g BID, Omeprazole 20 mg BID for 2 weeks. Vitamin Supplementation: Vit C (250 mg BID), Vit E (100 IU BID), Selenium (37.5 µg BID). Garlic Supplementation: Aged garlic oil 200 mg BID	H. pylori therapy for 2 weeks, vitamin & garlic for 7.3 years vs placebo	GC incidence, GC mortality
2.	Zhao et al. (2017) [26]	Randomized controlled trial	120 (Enteral nutrition: 40, Enteral nutrition	Enteral nutrition with fiber + probiotic: Inulin 10 g/day + Probiotic (Bifidobacteria	7-day intervention post-op	Diarrhea incidence, LOHS

			with fiber: 40, Enteral nutrition with fiber and probiotic: 40)	~10^9 CFU/day, Lactobacillus ~10^9 CFU/day) vs fiber only: Inulin 10 g/day vs standard formula: No added fiber/probiotic		
3.	Guo et al. (2020) [27]	Randomized controlled trial (secondary RCT)	3365 (Vitamin group: 1677, Placebo: 1688; Garlic group: 1678, Placebo : 1687)	Vitamin supplements: Vitamin C (250 mg BID), Vitamin E (100 IU BID), Selenium (37.5 µg BID). Garlic supplements: Aged garlic oil (200 mg BID).	22.3-year follow-up	GC incidence, GC mortality
4.	Zheng et al.	Randomized trial	100 (Probiotic : 50,	Probiotic mix: Bifidobacterium infantis (10^9	7–10 days post-op	Inflammatory markers, lymphocytes,

	(2019) [28]		Placebo: 50)	CFU), Lactobacillus acidophilus (10^9 CFU), Enterococcus faecalis (10^9 CFU), Bacillus cereus (10^8 CFU) administered 3 times/day vs Placebo		albumin, total protein
5.	Zhou et al. (2021) [29]	Randomized controlled trial	102 (High-Fiber Group: 51, Standard Diet Group: 51)	High-fiber dietary intervention: 25–30 g/day dietary fiber (from whole grains, legumes, vegetables, and fruits) vs Standard Diet (~10–12 g/day fiber)	12-week intervention	Systemic inflammatory markers (CRP, IL-6), SCFAs, GC risk markers

CFU = Colony-Forming Units, GC =Gastric Cancer, LOHS = Length of Hospital Stay, SCFA = Short-Chain Fatty Acids.

Table 2: Microbiome Alteration and Dietary Impact on Gastrointestinal Cancer Risk

	Author Name	Microbiome Involved	Microbiome Alteration	Result	
				Diet	Microbiome
1.	Li et al. (2019) [25]	H. pylori	Reduced H. pylori load, improved micronutrient status	Reduced GC incidence & mortality over 22 years	Reduced H. pylori load leading to improved microbiota status
2.	Zhao et al. (2017) [26]	Bifidobacteria, lactobacillus	Reduced pathogenic strains (clostridia), increased probiotic strains	Reduced diarrhea, shortened LOHS post-op	Increased probiotic strains, decreased pathogenic strains
3.	Guo et al. (2020) [27]	General gut microbiota.	Lifestyle factors modified microbiota (smoking & alcohol role)	Vitamin & garlic reduced GC mortality (enhanced benefit in	Changes in gut microbiota linked to vitamin & garlic intake

				non-alcohol drinkers)	
4.	Zheng et al. (2019) [28]	Bifidobacteria, lactobacillus, Akkermansia	Reduced Firmicutes/Bacteroidetes ratio, increased probiotic strains, decreased pathogenic strains	NA (no specific dietary intervention)	Reduced post-op inflammation, enhanced nutrition & immunity through probiotic-induced microbiota restoration
5.	Zhou et al. (2021) [29]	Bacteroides, Faecalibacterium, Akkermansia	Increased SCFA-producing strains, reduced pathogenic strains	High-fiber intake improved systemic inflammation and promoted gut barrier health	Favorable shift towards SCFA-producing microbiota, indicating reduced GC risk

CFU = Colony-Forming Units., LOHS = Length of Hospital Stay, SCFA = Short-Chain Fatty Acids

Table 3: Bias assessment using Jadad-style Risk of Bias tool:

	Author Name	Randomized	Randomization Method Appropriate	Double-Blind	Blinding Method Appropriate	Dropouts Described	Total Score
1.	Li et al. (2019) [25]	Yes	Yes	Yes	Yes	Yes	5
2.	Zhao et al. (2017) [26]	Yes	Yes	No	No	Yes	3
3.	Guo et al. (2020) [27]	Yes	Yes	Yes	No	Yes	4
4.	Zheng et al. (2019) [28]	Yes	Yes	Yes	Yes	Yes	5
5.	Zhou et al. (2021) [29]	Yes	Yes	No	No	Yes	3

Notes: Yes = 1 point, No = 0 point

Discussion

This systematic review brings together findings from five randomized controlled trials that collectively emphasize the emerging role of dietary and microbial interventions in the prevention, postoperative management, and long-term modulation of gastric cancer (GC) risk. Across these studies, interventions targeting gut microbiota, whether through antibiotics, fiber, vitamins, or probiotics, demonstrated measurable impacts on inflammation, microbial diversity, immune response, and clinical outcomes.

Li et al. [25] conducted one of the most significant long-term trials to date, spanning over 22 years in a high-risk population in Linqu County, China. Their study showed that *Helicobacter pylori* eradication using a two-week antibiotic regimen significantly reduced GC incidence and mortality. In addition, long-term vitamin supplementation (C, E, and selenium) resulted in a significant reductio n in cancer -related mortality, whereas garlic supplementation offered delayed but statist ically significant mortality advantages of the study.
These results uphold that early action and continued nutritional supp lementation are able to alter disease progress, especially among gr oups under the burden of dietary insufficiencies and endemic infection with H.pylori .

In a clinical setting, Zhao et al. [26] demonstrated that combining fiber and probiotics in enteral nutrition significantly reduced diarrhea and improved postoperative outcomes in gastric cancer patients. Compared to fiber-free or fiber-only regimens, the combined group showed faster restoration of gastrointestinal function and shorter hospital stays. This suggests that supporting the gut ecosystem during the critical postoperative window may improve patient recovery, reduce morbidity, and potentially influence long-term immune responses.

Zheng et al. [27] extended this understanding by showing that a multi-strain probiotic regimen in patients post-gastrectomy reduced inflammatory markers (e.g., leukocyte counts) and improved lymphocyte counts and nutritional markers (albumin and total protein). Microbial sequencing revealed increased beneficial bacteria such as *Akkermansia*, *Faecal bacterium*, and *Bacteroides*, alongside reduced harmful strains such as *Streptococcus*. These results provide mechanistic evidence that probiotics can reestablish microbial equilibrium and enhance host immunity, potentially buffering the adverse effects of surgical stress and dysbiosis.

Guo et al. [28] added an important behavioral dimension by assessing lifestyle interactions with nutritional supplementation. In a secondary analysis of the Shandong trial, they found that smoking independently increased both GC incidence and mortality. At the same time, the protective effect of garlic supplementation was notably more pronounced among non-alcohol users. This interaction suggests that behavioral factors such as tobacco and alcohol use may dampen the efficacy of chemo preventive interventions and should be considered when designing personalized preventive strategies.

Zhou et al. [29] specifically focused on the role of dietary fiber in modulating gut health and cancer risk in patients with precancerous gastric lesions. Participants on the high-fiber diet (~25–30 g/day) showed an increase in short-chain fatty acid (SCFA)-producing bacterial strains and a corresponding decline in pathogenic strains relative to the low-fiber diet (~10–12 g/day) group. These microbial alterations were associated with systemic anti-inflammatory actions, suggesting that gut microbial modification and immune control might prevent gastric cancer in at-risk individuals. The consumption of dietary fibre can prevent gastric cancer in a non-invasive and readily available manner.

These studies point to a paradigm shift in gastric cancer prevention and treatment, away from addressing onco genic infection alone or surgery towards h olistic approaches that utilize nutrition, microbiota, and behavior. Of equal significance is the gut microbiome's role in postoperative recovery and cancer prevention. Together with dietary fiber and probiotics, microbial balance has been found to be corrected, gastrointestinal complications improved, and immune and nutritional status improved. The high-fiber diet interventions promote an increase in beneficial SCFA-producing bacteria and reduce systemic inflammation and therefore the risk of malignant transformation in precancerous gastric lesions. The interventions discussed here not only modulate risk factors at a molecular level but also improve clinical outcomes and recovery. Additional interventions like long term supplements with vitamins and garlic extract have long-lasting protective effects on gastric cancer mortality, particularly in nutritionally susceptible individuals. Moreover, lifestyle habits like alcohol consumption and smoking may also influence the effectiveness of these interventions, pointing to the need for behaviour informed and tailored prevention approaches. Their effectiveness and long-term sustainability should be optimized in the future by making them more customized based on individual microbiome profiles, nutritional conditions, and lifestyle.

Conclusion:

Overall findings of these randomized controlled trials collectively offer strong evidence that microbial and dietary interventions play a major role in preventing and treating gastric cancer clinically. H. pylori eradication is still a cornerstone strategy, significantly reducing cancer incidence when applied early. In conclusion, the synthesis of diet, microbiome, and lifestyle interventions provides a comprehensive and realistic framework for the prevention of gastric cancer. Future prevention models must emphasize individualized, microbiome-targeted approaches to achieve optimal clinical impact and long-term success among high-risk groups.

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