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Research Article

Effects of red ginseng on gut microbiome in patients after gastrointestinal cancer surgery: A pilot, randomized controlled trial

Younsoo Seo [a], Ji Eun Jung [b], Seyeol Oh [b], In Gyu Kwon [b,*], Joon Seong Park [a,**]

[a] Department of Surgery and Cancer research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea
[b] Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Republic of Korea

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ABSTRACT

Background: The gut microbiome plays diverse roles in human health. Although Korean red ginseng (KRG) has shown therapeutic potential in animal models, its effects on the human gut microbiome after gastrointestinal (GI) cancer surgery remain underexplored. This prospective randomized controlled study aimed to evaluate postoperative safety of KRG and its impact on the gut microbiome and postoperative outcomes after GI cancer surgery.

Methods: Patients were randomly assigned 1:1 to the red ginseng or control groups. Microbiome analysis of preoperative and postoperative fecal samples was performed using *16S rRNA* sequencing. The alpha and beta diversities, taxonomic composition changes of microbiome, nutritional index, clinical symptoms, GI symptoms, and quality of life (QOL) were assessed.

Results: A total of 60 patients were enrolled and 16 patients in the red ginseng group and 25 in the control group were included in the final analysis. Postoperative alpha diversity decreased significantly in the control group, but remained relatively stable in the red ginseng group. Postoperative *Lactobacillus* levels increased significantly in the red ginseng group compared to the control group (18.34 % vs. 0.23 %; $p < 0.001$), whereas *Bifidobacterium* levels decreased ($p = 0.002$). Serum albumin levels were significantly higher in the red ginseng group at 3 months postoperatively ($p = 0.003$), and global health status/QOL scores were improved in the red ginseng group ($p = 0.047$).

Conclusion: Red ginseng supplementation may play a protective role in gut microbiome, improving clinical outcomes in patients undergoing GI cancer surgery, as a safe and supportive therapy for enhancing postoperative recovery.

1. Introduction

The microbiome refers to the collective community of microorganisms within a specific environment, including bacteria, viruses, fungi, and protozoans. The microbiome of the human gastrointestinal (GI) tract is estimated to contain approximately 100 trillion bacterial cells. This number exceeds the total number of host cells by a factor of 10, and the number of genes encoded by the gut microbiome is almost 100 times greater than the number encoded by the host [1]. This vast microbiome community is known to engage in complex interactions with the human host, particularly in relation to metabolism, nutrition, and immunity [2]. Various factors, including endogenous and exogenous changes, can influence the microbiome composition and function [3].

Surgery is one of the main factors affecting the microbiome, and gastrointestinal surgery,in particular, is among the most significant causes of dysbiosis (an imbalance in the microbial community) [4]. Perioperative antibiotics, surgical stress, tissue hypoxemia, and exposure to oxygen are possible contributing factors [5].Several studies have reported changes in species abundance and decreased microbiome diversity after stomach and colorectal surgery [6,7]. Furthermore, some studies have reported different microbiome compositions in patients with systemic inflammatory response syndrome compared with healthy volunteers [8,9]. These findings underscore the increasing importance of integrating microbiome research into clinical practice. Many patients

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* Corresponding author. Department of Surgery and Cancer Research Institute, Seoul National University College of Medicine 101 Daehak-ro, Chongno-gu, Seoul, 03080, Republic of Korea.
** Corresponding author.
E-mail addresses: surgeon@yuhs.ac (I.G. Kwon), jspark330@snu.ac.kr (J.S. Park).

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experience chronic GI disturbances, including abdominal distention, postoperatively [10]. Consequently, they often seek dietary supplements, including herbal medicines such as ginseng, to manage their symptoms.

Ginseng, an herbal medicine, is derived from *Panax ginseng*, an Asian ginseng species, and is processed into Korean red ginseng (KRG). The transformation of fresh ginseng into KRG generates unique bioactive components that are absent in fresh ginseng [11]. Although KRG is widely used as a health supplement, there is relatively little evidence for its efficacy. Ginseng is generally recognized for its antioxidant and anti-inflammatory properties, and its potential to enhance energy levels, making it a widely used traditional remedy in Asian countries [12]. Recent studies employing modern medical methodologies have demonstrated the therapeutic effects of KRG [13,14]. However, research on the association between ginseng and the microbiome has been predominantly conducted in animal models, with limited studies in humans. This lack of clinical validation regarding the safety and efficacy of ginseng has led to hesitancy among physicians regarding its integration into modern medical practice.

There is a paucity of research on the safety of red ginseng in the postoperative period and alterations in the microbiome associated with red ginseng consumption in patients after GI cancer surgery. We hypothesized that the consumption of KRG after GI cancer surgery is safe for patients and may influence the gut microbiome and enhance postoperative recovery and GI symptoms. To test this hypothesis, we conducted a single-center prospective randomized controlled trial. The aim of this study was to evaluate the safety and efficacy of red ginseng in patients who underwent gastrointestinal surgery, focusing on its effects on the balance and composition of the gut microbiome.

2. Materials and methods

2.1. Study design

This prospective, randomized controlled study was approved by the Institutional Review Board of Gangnam Severance Hospital (3-2022-0046) and performed in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained prior to patient enrollment. This work is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

"Eligible participants were adults aged between 18 and 79 years with an American Society of Anesthesiologists (ASA) physical status classification of I to III. All patients had pathologically confirmed GI cancer, including stomach and pancreatic cancers, and were scheduled to undergo curative resection without prior neoadjuvant chemotherapy.

Patients were excluded if they had a history of underlying GI diseases, such as inflammatory bowel disease, ulcerative colitis, megacolon or megarectum, galactose intolerance, lactase deficiency, glucose–galactose malabsorption, short bowel syndrome, hereditary bowel diseases, or autoimmune disorders. Additional exclusion criteria included inability to ingest oral red ginseng extract or maintain a normal diet; history of prior abdominal radiation or chemotherapy; preoperative bowel obstruction or the need for ileostomy or colostomy formation after surgery; and uncontrolled diabetes mellitus, liver cirrhosis, or renal failure. Patients who required antibiotic treatment for more than 2 weeks during hospitalization, had known allergic reactions to red ginseng, or had used probiotics or prebiotics within 3 months before enrollment (or were unwilling to abstain from them during the study period) were also excluded."

2.2. Randomization

Patients were randomly assigned to the red ginseng and control groups in a 1:1 ratio. Randomization was performed using a computer-generated method based on tables from the Sealed Envelope website (https://www.sealedenvelope.com/). To achieve balanced group sizes, randomization was stratified according to the surgery type (gastrectomy or pylorus-preserving pancreaticoduodenectomy). The study medication (KRG extract) was administered by a research nurse. The physicians who managed the patients postoperatively were blinded to the group allocation and study protocol.

The sample size calculation was based on a pilot trial. For microbiome analysis, a minimum of 20 participants is recommended and a previous study on red ginseng was conducted with 13 participants per group (26 total), we calculated the sample size with a 2-sided α value of 5 %, 80 % power, and a 20 % dropout rate. The required sample size was 26 participants for each intervention group. Therefore, the total number of participants recruited was 60.

2.3. Intervention

The KRG extract tablets (500 mg per tablet, red ginseng; Jung-Kwan-Jang, South Korea) used in this study contained 6-year-old red ginseng extract powder with ginsenosides Rg1 + Rb1 + Rg3 at 7 mg/g in the solid portion, along with sucrose fatty acid ester, stearic acid, and hydroxypropyl methylcellulose. The intervention group received 2 tablets of KRG extract twice daily, whereas the control group did not receive any KRG.

The starting point of medication intake was the first outpatient visit after discharge, typically 4 weeks postoperatively, following confirmation of the absence of surgical complications. The medication was administered continuously for 2 months.

Physical measurements, blood tests, stool sampling, and clinical symptom questionnaires were conducted twice: before surgery and 2 months after the start of medication intake (approximately 3 months post-surgery). Medication compliance was monitored by having patients return the remaining tablets after the 2-month medication period, with the research nurse counting the returned tablets. The study protocol was registered at ClinicalTrials.gov (NCT06561516).

2.4. Sampling

Blood and stool samples were collected from patients prior to surgery. Three months after surgery, blood samples and stool specimens were collected from patients in both the red ginseng and control groups. Patients were considered compliant and included in the study if they consumed at least 75 % of the total prescribed KRG extract over a 3-month period.

2.5. Microbiome analysis

Frozen stool samples collected from participating patients were sent to a contracted laboratory for next-generation sequencing. For bacterial profiling, polymerase chain reaction amplification was performed using fusion primers targeting the V3–V4 regions of the 16S ribosomal ribonucleic acid (rRNA) gene. Sequencing was conducted at CJ Bioscience, Inc. (Seoul, Korea) using an Illumina MiSeq platform (Illumina, San Diego, CA, USA) according to the manufacturer's protocol. The raw sequencing reads were processed to ensure quality control. Unique reads were extracted and redundant sequences were clustered with unique reads using the derep_fulllength command. Taxonomic assignment was performed against the EzBioCloud 16S rRNA database using the usearch_global command in VSEARCH, followed by precise pairwise alignment. All analyses were conducted using the EzBioCloud 16S-based MTP platform, a bioinformatics cloud system provided by CJ Bioscience, Inc [15].

2.6. Outcomes

Preoperative physical examinations and blood tests, including lymphocyte count and serum albumin and total cholesterol levels, were conducted. Clinical GI symptoms, quality of life, and defecation were assessed using a questionnaire. The condition of the patients was assessed before surgery, after surgery (prior to the intervention), and after completion of the medication.

The primary outcomes included microbiome analysis, focusing on the diversity of the gut microbiome and changes in its taxonomic composition. Secondary outcomes included the assessment of nutritional status and clinical GI symptoms using a questionnaire.

2.6.1. *Alpha diversity*

Alpha diversity is a measurement of microbial diversity within a sample, including measurements of richness and evenness measurements [16]. We utilized several alpha diversity indices, including observed operational taxonomic units (OTUs), Chao1, abundance-based coverage estimator (ACE), and Jackknife as species richness indices, and Simpson, NPShannon, and Shannon as evenness indices. In addition, phylogenetic diversity was analyzed.

2.6.2. *Beta diversity*

Beta diversity is a measure of differences in the microbiome among samples [16]. We analyzed beta diversity to compare the gut microbiome across different groups and time points. We used the Bray-Curtis dissimilarity index to quantify the compositional differences. Principal coordinate analysis (PCoA) was employed to visualize beta diversity patterns. The statistical significance of the observed differences was assessed using the permutational multivariate analysis of variance test (PERMANOVA). Statistical significance was set at $p < 0.05$.

2.6.3. *Taxonomic composition*

The composition of the microbiome at the phylum, order, and genus levels was analyzed in each group. The relative abundances of the selected species were also analyzed between the 2 groups, both preoperatively and postoperatively.

2.6.4. *Nutritional status index*

Body weight, lymphocyte count, serum albumin level, and serum total cholesterol level were measured preoperatively and postoperatively to assess the patients' nutritional and biochemical status. Blood samples were collected 1 and 3 months postoperatively to monitor these parameters over time.

2.6.5. *Clinical GI functions and related quality of life*

To measure changes in bowel and GI symptoms experienced by patients after GI surgery and to evaluate postoperative quality of life, the following questionnaires were utilized: GI symptom questionnaires, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire-Stomach (QLQ-STO22). Additionally, the Low Anterior Resection Syndrome (LARS) score questionnaire was used to assess bowel dysfunction in patients following lower anterior resection for rectal cancer. Questionnaire results were analyzed preoperatively and at 3 months postoperatively (after 2 months of medication intake).The utilized questionnaires are supplemented as supplementary materials in English version (Supplementary material 1).

2.6.6. *Adverse effects*

Adverse effects of red ginseng were monitored through laboratory evaluations, including renal function tests, liver enzyme levels, and hematologic parameters such as cytopenia, as well as observation for allergic reactions. Some gastrointestinal symptoms or general conditions could not be clearly distinguished from postoperative effects. Therefore, behavioral or subjective symptoms were not classified as adverse events but were instead recorded and analyzed through patient-reported questionnaires.**2.7. Statistical analysis**.

All statistical analyses were performed using SPSS version 29.0.2.0 (IBM Corp., Armonk, NY, USA). The Mann-Whitney U test was used for between-group comparisons and the Wilcoxon signed-rank test was used for within-group comparisons. Statistical significance was set at $p < 0.05$.

3. Results

A total of 60 patients were enrolled and randomly assigned to the intervention group in a 1:1 ratio. As 1 patient was excluded because of advanced disease, 29 patients were allocated to the red ginseng group and 30 to the control group. Throughout the study, an additional 18 patients (13 from the red ginseng group and 5 from the control group) dropped out due to insufficient ginseng intake, study withdrawal, or death. The final analysis included 16 and 25 patients in the red ginseng and control groups, respectively. The CONSORT algorithm used in this study and participant allocation are illustrated in the flowchart in Fig. 1.

3.1. *Baseline demographics and clinical characteristics*

The baseline characteristics of the study participants are summarized in Table 1. The sex distribution was similar between the 2 groups, with 68.8 % females in the red ginseng group and 60.0 % in the control group ($p = 0.570$). The mean age was also similar between the groups (59.5 ± 11.4 years for the red ginseng vs. 59.2 ± 12.6 years for the control group; $p = 0.931$). A significant difference was observed in BMI between groups, with the red ginseng group having a higher mean BMI (24.9 ± 2.9 kg/m^2) than the control group (23.0 ± 2.1 kg/m^2; $p = 0.018$). Other variables related to baseline nutritional status, including the prevalence of postoperative complications, diabetes mellitus, baseline total protein level, albumin level, lymphocyte count, and total cholesterol level, showed no statistically significant differences between the groups.

All patients in the Red Ginseng group were diagnosed with gastric cancer, whereas the control group included patients with both gastric (n = 18) and pancreatic cancers (n = 7); however, the difference was not statistically significant ($p = 0.058$).

3.2. *Adverse effects*

No adverse effects associated with KRG consumption have been reported. None of the patients exhibited abnormal responses or laboratory findings related to red ginseng intake.

3.3. *Alpha diversity*

The alpha diversity of the gut microbiome was assessed in the red ginseng and control groups, both preoperatively and postoperatively. Both the red ginseng and control groups showed a decrease in overall alpha diversity, but intergroup comparisons showed no significant differences in any of the alpha diversity indices between the red ginseng

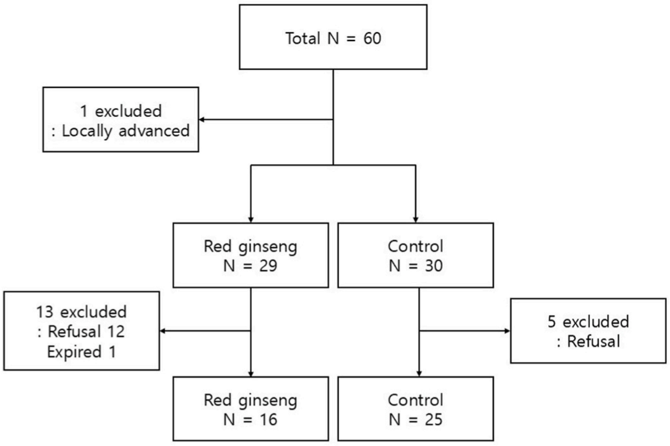

Fig. 1. CONSORT algorithm.

Table 1
Baseline demographics and clinical characteristics.

Variables	Red ginseng (n = 16)	Control (n = 25)	P-value
Gender (Female) (n (%))	11 (68.8 %)	15 (60.0 %)	0.570
Age (mean ± SD, yrs)	59.5 ± 11.4	59.2 ± 12.6	0.931
BMI (mean ± SD, kg/m^2)	24.9 ± 2.9	23.0 ± 2.1	0.018[a]
DM (n (%))	1 (6.3 %)	5 (20.0 %)	0.376
Diagnosis			
Gastric cancer (n (%))	16 (100 %)	18 (72 %)	0.058
Pancreatic cancer (n (%))	0	7 (28 %)	
Postoperative complication (n (%))	0 (0.0 %)	4 (16.0 %)	0.143
Total protein (mean ± SD, g/dL)	7.2 ± 0.4	7.2 ± 0.6	0.736
Albumin (mean ± SD, g/dL)	4.4 ± 0.3	4.3 ± 0.3	0.228
Lymphocyte counts (mean ± SD,/uL)	2270.0 ± 736.9	2099.6 ± 653.6	0.443
Total Cholesterol (mean ± SD, mg/dL)	180.3 ± 40.8	170.4 ± 43.5	0.471

[a] P-value <0.05 with statistical significance.

group and control groups, or between the preoperative and postoperative status of each group (Fig. 2).

Subsequently, paired pre- and postoperative samples from individual participants were analyzed (Table 2). In the control group, significant reductions were observed in several alpha diversity indices postoperatively, indicating a decrease in diversity, which is generally considered unfavorable. Specifically, the number of observed OTUs decreased significantly from a median of 324.00 (interquartile range [IQR], 229.50–388.50) to 261.00 (IQR, 211.50–336.00) ($p = 0.046$). The NPShannon index value decreased significantly from 3.06 (IQR, 2.34–3.42) to 2.35 (IQR, 2.13–2.82) ($p = 0.025$). The Shannon index value also decreased significantly from 3.05 (IQR, 2.33–3.41) to 2.33 (IQR, 2.11–2.81) ($p = 0.023$). In contrast, the red ginseng group did not exhibit significant changes in most alpha diversity indices postoperatively, except for ACE, (decreased from 474.68 [IQR, 418.22–550.06] to 338.02 (IQR, 306.23–462.44) ($p = 0.039$). Although there were reductions in postoperative index values in this group, these changes were not statistically significant.

Overall, these results suggested that while the control group experienced significant reductions in several key alpha diversity index values postoperatively, the red ginseng group maintained stable diversity levels, indicating a potentially protective effect of red ginseng on the gut microbiome following surgery.

3.4. *Beta diversity*

We performed beta diversity analysis using the Bray-Curtis dissimilarity method to compare the microbiome composition between the groups, both preoperatively and postoperatively. The PCoA plots illustrating these differences are shown in Fig. 1. No significant differences were observed between the red ginseng and control groups, either preoperatively ($p = 0.229$) or postoperatively ($p = 0.279$). However, significant within-group changes in beta diversity were detected from the preoperative to postoperative period in both the red ginseng group ($p < 0.001$) and the control group ($p < 0.001$). These findings suggest that surgical stress induces substantial alterations in microbiome composition.

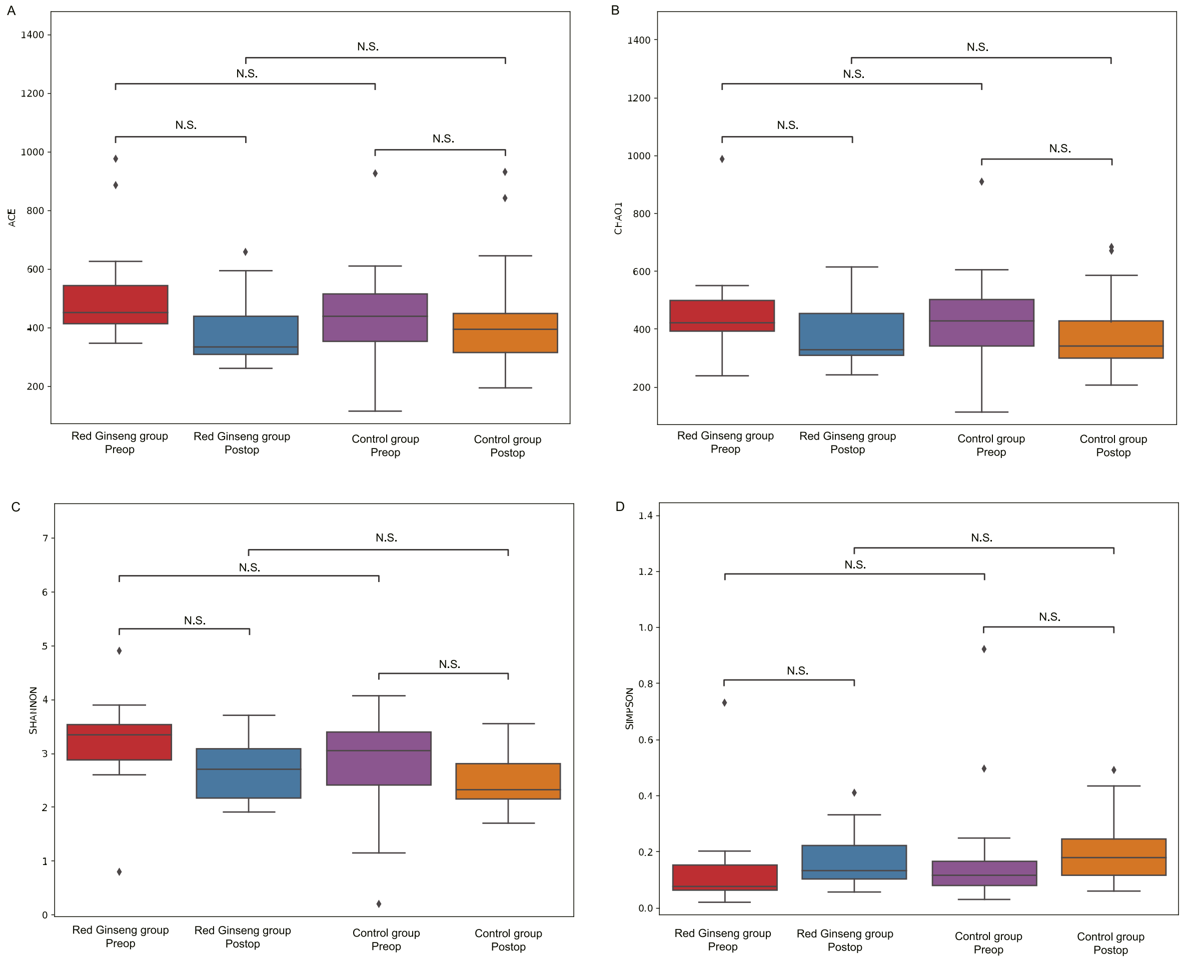

Fig. 2. Alpha diversity indices. (A) ACE (B) CHAO1 (C) Shannon (D) Simpson. (N.S., not significant, Mann–Whitney *U* test.

Table 2

Alpha diversity index: pairing preoperative and postoperative samples of individual participants.

	Red ginseng			Control		
Index Median (IQR)	preoperative	postoperative	p-value	preoperative	postoperative	p-value
ACE	474.68 (418.22–550.06)	338.02 (306.23–462.44)	0.039[a]	445.71 (316.01–528.38)	353.24 (310.78–490.03)	0.476
Chao1	435.78 (397.95–495.53)	330.39 (299.72–466.62)	0.098	421.66 (298.82–488.25)	342.07 (292.95–439.92)	0.367
Jackknife	467.52 (424.50–527.93)	367.94 (314.61–535.46)	0.134	445.54 (314.61–535.46)	367.95 (310.03–482.60)	0.459
Observed OTUs	351.50 (312.25–410.25)	255.50 (219.50–337.50)	0.056	324.00 (229.50–388.50)	261.00 (211.50–336.00)	0.046[a]
NPShannon	3.36 (2.85–3.58)	2.72 (2.11–3.19)	0.079	3.06 (2.34–3.42)	2.35 (2.13–2.82)	0.025[a]
Shannon	3.34 (2.84–3.56)	2.71 (2.10–3.17)	0.079	3.05 (2.33–3.41)	2.33 (2.11–2.81)	0.023[a]
Simpson	0.08 (0.06–0.16)	0.13 (0.09–0.22)	0.301	0.11 (0.08–0.19)	0.18 (0.12–0.28)	0.061
Phylogenetic Diversity	588.50 (545.50–678.75)	478.50 (400.75–612.75)	0.109	562.00 (414.50–669.00)	476.00 (408.50–577.00)	0.101
Good's coverage of library(%)	99.77 (99.71–99.84)	99.78 (99.69–99.81)	0.796	99.78 (99.71–99.85)	99.76 (99.70–99.84)	0.242

[a] P-value <0.05 with statistical significance.

3.5. *Taxonomic composition*

3.5.1. *Composition proportion*

The taxonomic composition changes in each group at the phylum, order, and genus levels are shown in Fig. 2. Overall, at the phylum level, both the red ginseng and control groups exhibited an increase in the proportion of *Proteobacteria* after surgery, accompanied by a decrease in the proportion of *Firmicutes*, *Actinobacteria*, and *Bacteroidetes* (Fig. 2A). At the order level, the notable changes included a postoperative reduction in the proportions of *Bifidobacteriales* and *Bacteroidales*. Specifically, *Lactobacillales* showed a decreasing trend in the control group but an increasing trend in the red ginseng group after surgery (Fig. 2B). A similar trend was observed at the genus level, with *Lactobacillus* exhibiting an increased proportion in the red ginseng group (Fig. 2C).

3.5.2. *Species relative abundance*

We focused on specific genera known for their beneficial roles in the host, including *Lactobacillus* and *Bifidobacterium*, as well as *Clostridium*, *Escherichia*, and *Staphylococcus*, which are often associated with pathological conditions [17,18]. The relative abundances of these taxa are summarized in Fig. 3. The preoperative baseline proportion of each taxon was similar between the red ginseng and control groups. The analysis revealed significant differences in the relative abundance of certain taxa between the red ginseng and control groups, particularly during the postoperative period. Notably, the postoperative proportion of *Lactobacillus* increased significantly in the red ginseng group compared to the control group (18.34 % vs. 0.23 %; $p < 0.001$). In contrast, the postoperative proportion of *Bifidobacterium* decreased significantly in the ginseng group (0.32 % vs. 2.27 %; $p = 0.002$). For *Staphylococcus*, *Enterococcus*, and *Clostridium*, there were no statistically significant differences between the intervention groups; however, the red ginseng group showed a greater decrease in the proportions of these three species.

Additionally, the relative abundance of *Akkermansia muciniphila*, one of mucus-degrading bacteria, was analyzed in Fig. 4. Decrease in *Akkermansia muciniphila* is associated with inflammatory bowel disease, obesity and metabolic syndrome [19–21]. Both preoperatively and postoperatively, the red ginseng group and control group showed no significant difference in the relative abundance of *Akkermansia muciniphila* (median, preoperative 1.05 % vs. 0.65 % ($p = 0.194$); postoperative 0.02 % vs. 0.01 % ($p = 0.368$). Besides, there were same trends in both groups, showing postoperative decrease of *Akkermansia muciniphila* relative abundance, but without statistical significance. (red ginseng: $p = 0.194$, control: $p = 0.701$).

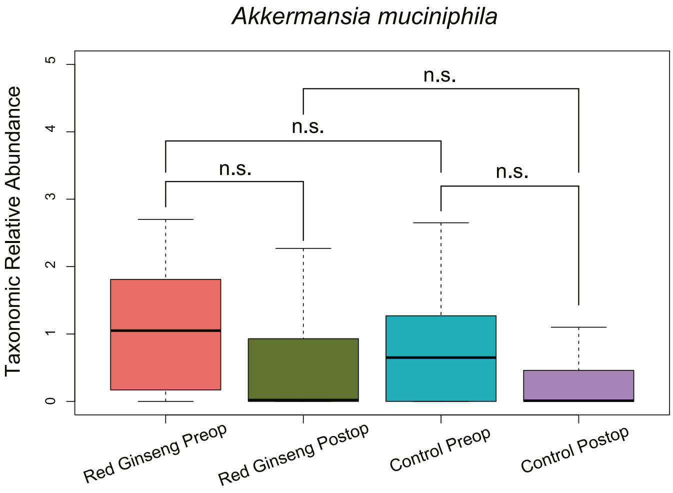

Fig. 4. Relative abundance of *Akkermansia muciniphila* (Mann–Whitney *U* test).

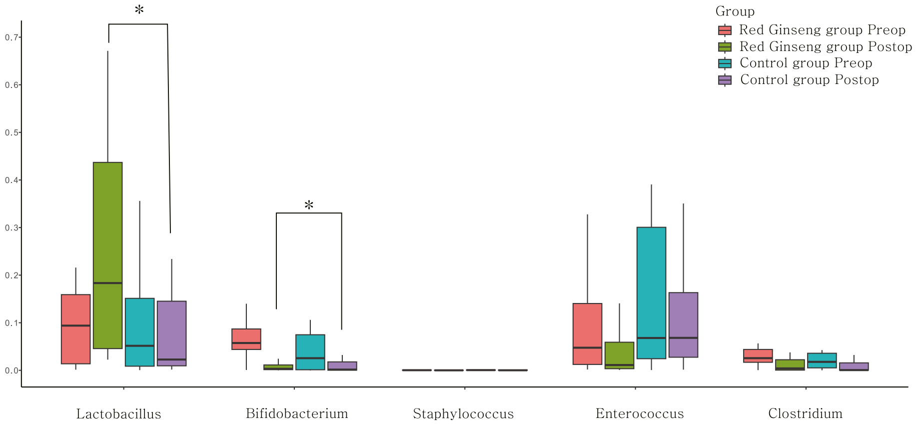

Fig. 3. Relative abundance of specific genera: *Lactobacillus*, *Bifidobacterium*, *Staphylococcus*, *Enterococcus*, and *Clostridium*. (Mann–Whitney *U* test).

3.6. Nutritional index

Nutritional indicators for each group were analyzed. Initially, there was a significant difference in BMI between the red ginseng and control groups at baseline (24.9 vs. 23.0; $p = 0.018$). Postoperatively, the BMI reduction, as an indicator of nutritional status, showed no significant difference between the groups, with a mean reduction of 2.0 ± 0.2 in the red ginseng group and 1.7 ± 0.3 in the control group ($p = 0.469$). Similarly, weight loss did not show a significant difference between the groups (5.4 ± 0.6 kg vs. 4.7 ± 0.7 kg; $p = 0.239$).

Serum laboratory tests were also used to compare nutritional status. One month postoperatively, there were no significant differences in serum albumin, lymphocyte, or total cholesterol levels between the groups. However, at 3 months postoperatively, the serum albumin levels were significantly higher in the red ginseng group than the control group (4.3 ± 0.1 g/dL vs. 4.1 ± 0.3 g/dL, $p = 0.003$).

3.7. Clinical GI function and related quality of life

Three months after surgery, the patients completed questionnaires, and the results from 40 patients were retrieved and analyzed. There were fewer daily gas passes in the red ginseng group than the control group (median 6.7 vs. 11.8 times/day; $p = 0.011$), but no significant postoperative differences in other clinical symptoms were observed between the intervention groups, including nausea or vomiting, constipation, diarrhea, fatigue, abdominal distension, or gas odor.

There was no significant difference in the postoperative global health status/QOL score between the intervention groups (red ginseng 71.9 vs. control, 65.3); however, the difference in global health status/QOL score between the preoperative and postoperative assessments was significantly different, showing enhancement in the red ginseng group (+4.2 vs. −14.7; $p = 0.047$).

4. Discussion

Colonization of the human gut microbiome begins at birth. The neonatal gut is considered to be sterile and it contains few microorganisms at birth [22]. However, the composition of the gut microbiome changes over time because of various factors, such as genetics, breastfeeding, dietary patterns, and exposure to numerous external and internal host factors, which complicates the analysis [23,24].

Recent studies have suggested that the gut microbiome significantly influences host function, leading to the hypothesis that it can be considered as a functional organ of the host [1]. The functions of the gut microbiome include energy production through the metabolism of non-digestible carbohydrates, such as large polysaccharides, mucin, and unabsorbed sugars. It also plays a role in host protection, the immune response, allergy prevention, and stress reactivity through bidirectional communication along the gut-brain axis [25–30].

This study investigated the effects of red ginseng consumption on the gut microbiome of patients who underwent radical surgery for GI cancer. Our findings indicated that KRG may play a protective role in maintaining the diversity of the gut microbiome and enhancing postoperative recovery.

A key observation from our study is that red ginseng supplementation did not adversely affect the course of postoperative patients, but it helped preserve the postoperative alpha diversity of the gut microbiome. Beta diversity analysis revealed significant changes in both groups from the preoperative to postoperative timepoint, reflecting the substantial impact of surgical stress on microbiome composition. Although the control group experienced significant reductions in several alpha diversity index values, indicative of a less diverse and potentially less resilient gut microbiome, the red ginseng group maintained relatively stable diversity. This suggested that red ginseng may mitigate the adverse effects of surgical stress on gut microbiome diversity.

This finding is consistent with those of the previous studies. In a murine model, Lee et al. (2021) demonstrated that supplementation with a saponin-containing red ginseng extract and a saponin-depleted red ginseng extract effectively prevented or reversed alterations in the gut microbiota composition induced by a high-fat diet. This study revealed significant changes at the phylum level. Specifically, stool samples from the murine group that received the saponin-containing ginseng extract exhibited an increase in the abundance of *Verrucomicrobia* and a decrease in the abundance of *Proteobacteria* and *Deferribacteres*. Conversely, the group supplemented with the saponin-depleted ginseng extract showed an increase in the abundance of *Proteobacteria* and a decrease in the abundance of *Verrucomicrobia*. These findings suggest that different components of ginseng extracts can lead to distinct alterations in the composition of the gut microbiota [31].

Our taxonomic analysis highlighted significant postoperative changes in the proportions of specific taxa. Notably, the proportion of *Lactobacillus*, a genus known for its beneficial effects on gut health, significantly increased in the red ginseng group. This increase suggests a potential prebiotic effect of red ginseng, promoting the growth of beneficial bacteria. The improved postoperative albumin level, global health status/QOL score and less frequent gas passing in the red ginseng group may explain this result.

Although the precise mechanisms remain to be fully elucidated, red ginseng is thought to influence the gut microbiota through several biological pathways. First, ginsenosides can be metabolized by intestinal bacteria, and this biotransformation selectively promotes ginsenoside-metabolizing taxa and facilitates the generation of bioactive metabolites [32–34]. Second, red ginseng has been associated with an increase in short-chain fatty acid–producing bacteria, which support intestinal barrier integrity and mucosal homeostasis [35,36]. Third, ginsenosides exert anti-inflammatory and immunomodulatory effects, including modulation of NF-κB signaling and cytokine responses, which may indirectly influence microbial composition [37]. Collectively, these mechanisms suggest that both direct microbial biotransformation and host-mediated pathways contribute to red ginseng-related microbiome modulation. However, the detailed directionality and dynamics of these microbial shifts require further investigation in more complex clinical and mechanistic settings.

Primary mechanism by which ginseng regulates specific microbial species is poorly understood. However, its effect on the upregulation of *Lactobacillus* and *Bifidobacterium* has been repeatedly documented and affirmed by numerous studies [38,39]. The potential active components include ginsenosides, which are steroid-like saponins unique to ginseng species, and ginseng polysaccharides, which are abundant active substances released during cell wall deconstruction [40,41]. Previous studies have shown that the levels of ginseng polysaccharides positively correlate with the abundance of *Lactobacillus* [42]. Microbial metabolism plays a key role in disease progression, and various bacterial species contain enzymes involved in the deglycosylation of glycosides. For example, *Bifidobacterium* species catalyze the deglycosylation of saponin glycosides through beta-glycosidase activity [43]. Ginseng polysaccharides can interact as metabolites with specific microbiome species, thereby modulating their abundance.

However, in the present study, *Lactobacillus* and *Bifidobacterium* showed different regulatory tendencies. Both strains are non-spore-forming, gram-positive, lactic-acid-producing bacteria, but they belong to 2 different phyla: *Firmicutes* and *Actinobacteria*. *Lactobacilli* ferment refined sugars to produce lactic acid, but they have limited biosynthetic ability compared to *Bifidobacterium* species, which play a major role in producing short-chain fatty acids [44]. Both genera have validated probiotic potential and immunomodulatory properties [44–46]. Most studies have reported the upregulation of *Bifidobacterium* with ginseng supplementation. The specific mechanism underlying the decrease in *Bifidobacterium* abundance observed in this study remains unclear, necessitating further studies and theoretical groundwork. A possible hypothesis is that differences in ginseng processing methods alter their components and impact the microbiome species [38]. Additionally, the contrasting responses of *Lactobacillus* and *Bifidobacterium* to the KRG extract might be due to differences in their metabolism pathways. In addition, the explosive increase in *Lactobacillus* may have competitively slowed the increase in *Bifidobacterium* abundance; however, further research is needed to confirm this hypothesis. As a subanalysis, we conducted a co-occurrence network analysis among the gut microbial taxa from this study to identify potential relationships and interactions between different taxa at the species level (Fig. 3). In this network, *Lactobacillus* and *Bifidobacterium* did not show significant interactions, but the network still showed that the microbiome was composed of highly complex interactions and not only simple linear relationships among species, which explains the difficulty with interpreting microbiome data. Also, some *Bifidobacterium* strains possess mucolytic properties, similar to *Akkermansia muciniphila*, which is considered one of the next-generation probiotics [47]. In this study, *Akkermansia muciniphila* did not show a statistically significant change in its relative abundance. However, as the two strains exhibited a positive correlation in the co-occurrence network (Fig. 3), this relationship should be taken into account when interpreting changes in *Bifidobacterium* abundance. A previous study suggested that enrichment of *Akkermansia muciniphila* in the mouse model of inflammatory bowel disease, developed colitis, due to the mucus-degrading characteristics of *Akkermansia* strain [48]. Therefore, *Bifidobacterium* strain in microbiome analysis should be interpreted in caution, integrating in its clinical application.

These findings have important clinical implications. First, red ginseng supplementation may be considered an adjunctive therapy to safely support gut microbiome health and diversity in patients undergoing major GI surgery. Maintaining a diverse gut microbiome is essential to prevent postoperative complications and promote overall health. It can also improve the levels of *Lactobacillus*, leading to better clinical GI symptoms and improved nutritional status, such as appropriate serum albumin levels, thereby reducing the risk of malnutrition-related complications. This is particularly important in patients with cancer who have a higher risk of malnutrition.

Our study has several limitations. The relatively small sample size and variability in the baseline microbiome composition may limit the validity of our findings. Among a total of 59 participants, 18 dropped out, which was relatively high. One patient died due to a postoperative complication, while the others withdrew because of unwillingness to adhere to the study protocol, mainly related to refusal to provide fecal samples or low compliance with ginseng intake. Future studies with larger cohorts and longer follow-up periods are required to confirm these results and further explore the mechanisms underlying the observed effects. In addition, the specific pathways through which red ginseng affects the gut microbiome and nutritional status remain unclear. Further research is required to investigate the bioactive compounds in red ginseng and their interaction with the gut microbiome. Also, another limitation is the challenge of distinguishing postoperative recovery-related changes from treatment effects of red ginseng. Although randomization helped balance postoperative influences across groups and several clinically meaningful parameters demonstrated significant differences, potential overlap between surgical recovery effects and intervention effects cannot be completely excluded.

Finally, the lack of precision in defining the microbiome distribution represents another limitation of our study and remains an underexplored area in microbiome research. Because the individual microbiome varies with age, baseline environment, and dietary habits, controlling these factors is challenging [49]. Furthermore, the biological complexity of the microbiome is not fully understood, leading to divergent views on analytical methods and opinions on which microbiome states are healthy for the host [50]. Further research on the human microbiome is needed to advance this field. Such studies are essential to enhance our understanding of complex interactions within the microbiome and their implications for human health.

5. Conclusions

In this pilot randomized controlled trial, red ginseng supplementation following gastrointestinal cancer surgery was safe and did not result in adverse postoperative effects. Patients receiving red ginseng demonstrated relative preservation of gut microbiome diversity compared with controls, with a significant postoperative increase in Lactobacillus abundance. In addition, patients in the red ginseng group showed improved serum albumin levels and better recovery of global health status and quality of life.

These findings suggest that red ginseng may help stabilize postoperative gut microbiome composition and support nutritional and functional recovery after major gastrointestinal surgery. Further large-scale studies with longer follow-up are warranted to validate these results and elucidate the underlying mechanisms of microbiome modulation.

Disclosure

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Appendix A. Supplementary data

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