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Trends in Current Clinical Research on Herbal Medicines and Gut Microbiota

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Abstract: *Gut microbiota, regarded as the second genome of the human body, has become a key modulator of cancer treatment. It is an emerging topic in precision medicine, and many studies have reported that the variability in most diseases and individuals is related to gut microbiota characteristics. Numerous clinical studies on cancer treatment have demonstrated a correlation between therapeutic responses to immunotherapeutic cancer drugs and gut immunity or the microbiome. In this paper, we present the current clinical research on herbal medicines and gut microbiota and explore the possibility of integrative cancer treatment with herbal medicines and immunotherapeutic cancer drugs. We identified six clinical trials enrolled in the Clinical Research Information Service and five clinical studies on gut microbiota and herbal medicines in MEDLINE via PubMed. Generally, clinical studies have used 16S rRNA sequencing to analyze the gut microbiota. Study findings have suggested that the gut microbiota can be used as a biomarker to predict the pharmacological effects of herbal medicines. Gut microbiota modifications by herbal medicines may inhibit tumor progression. Herbal medicines are metabolized to active substances through interactions with the microbiome and control the dysbiosis of the gut microbiome. Further research on the possibility of individualized precision medicine by analyzing the gut microbiota after administering herbal medicine is needed.*

Keywords: Clinical trial, Gut microbiota, Herbal medicine, Precision medicine, Review

1. Introduction

The gut microbiota has emerged as a top research topic since human health and gut microbiota interactions have been revealed. The gut microbiome is a complex community of microorganisms in the gastrointestinal (GI) tract [1]. Gut microbiota analysis has been suggested to provide strong evidence for personalized treatments and precision medicine [2]. In cancer treatment, higher fecal microbial diversity has been associated with longer progression-free survival (PFS) [3]. Furthermore, high abundances of *Faecalibacterium* and *Bacteroidales* were reported in responders and non-responders, respectively [3]. In a phase I clinical trial of 10 patients, two partial responses and one complete response were observed after fecal microbiota transplantation from donors who had achieved a complete response at least 1 year after being treated with anti–PD-1 monotherapy for metastatic melanoma, suggesting the possibility of fecal microbiota transplantation in cancer therapy [4]. Since each person has a different gut microbiome and the abundance of certain microbiomes is correlated with the response to immune checkpoint inhibitors [5], the human gut microbiota profile is a promising source of evidence for individualized cancer treatment.

Traditionally, personalized medicine has been recognized as an advantage of traditional medicine that differs from Western medicine [6]. Although the standardization of Korean Medicine treatment has been promoted with the development of clinical practice guidelines in recent years, the unique constitutional medicine and pattern diagnosis of Korean medicine indicate that the patient is also an important factor in treatment [7]. Doctors of Korean Medicine accurately identify a patient's individual characteristics through

history taking and physical examination and determine the appropriate individualized treatment [8]. Herbal medicine, the primary treatment modality in Korean Medicine, is derived from a composition of multiple medicinal herbs, which may be added or removed based on a single prescription by a doctor of Korean Medicine. Because herbal medicines are primarily absorbed and excreted from the gut through oral administration, evidence that herbal medicines can modulate the gut microbiome is key to novel evidence-based personalized treatment [9].

Herbal medicines have been suggested to affect the gut microbiota via absorption through active small molecules or by changing the composition of the gut microbiota and its secretions [10]. Previous experimental studies on herbal medicines and gut microbiota have mainly focused on metabolic and intestinal diseases, such as obesity, diabetes, and irritable bowel syndrome [11, 12]. Studies have reported the potential of fermented herbal extracts in the treatment of lower gastrointestinal symptoms [13]. However, the clinical efficacy and mechanisms of action of herbal medicines on the gut microbiota remain unknown. In the present study, we explored recent domestic clinical trials on gut microbiota and herbal medicine and suggested further research, especially focusing on cancer.

2. Materials and Methods

2.1 Data sources and searches

We searched enrolled clinical trials with topic including “gut microbiota” in Korean in Clinical Research Information Service (CRIS), an online registration flatform for registration of clinical trials operated by Korea Disease Control and Prevention Agency. Clinical trials of herbal medicine with analysis of gut microbiome were screened in MEDLINE via Pubmed by following search strategy: (“microbiome” OR “microbiota”) AND “herbal medicine” without any filterations. The search was conducted on June 16, 2023.

2.2 Inclusion criteria

We considered the participants, interventions, controls, outcomes, and study designs as the inclusion criteria. There were no restrictions on the participants or controls. The interventions included herbal medicines without any limitation on medication types. For outcomes, we selected studies that analyzed the gut microbiota. We included all clinical studies regardless of the study design.

2.3 Data extraction

The data extraction form included the study design, participants, sample size, intervention, controls, outcomes, current status of the trial, and methods of gut microbiome analysis. The data were extracted by one author (EC) and reviewed by another (MKJ). Discrepancies were resolved through discussions within the authors’ research group. Microsoft Excel software 16.0 and Zotero were used in the data selection and coding process.

3. Results

Registered clinical trials primarily state the methods, whereas PubMed presents research articles. Therefore, we organized the studies from PubMed and CRIS registrations into separate tables.

3.1 Clinical trials on herbal medicine analyzing gut microbiome registered in PubMed

From PubMed, five clinical trials on gut microbiota and herbal medicine were identified. The most recent study was a clinical study on *Inchinkoto*, which contained geniposide, a precursor of genipin (converted by gut microbiota) with choleretic activity [14]. The diversity of the gut microbiome was evaluated using the Shannon-Weiner index. Based on the correlation between stool genipin-producing activity and the microbiome profile, the study suggested that modifying the gut microbiome could be a target for improving the pharmacological effect of *Inchinkoto* [14]. In a prospective randomized study [15], *Daikenchuto* was used in patients who underwent laparoscopic colectomy for left-sided colon cancer, and the gut microbiome was analyzed as the second endpoint. Although the postoperative gut microbiota showed no difference between the *Daikenchuto* and non-*Daikenchuto* groups, the *Daikenchuto* group showed faster recovery of fecal DNA concentration after surgery [15]. In another clinical study, the combination group of *Jianpi Qinghua* with proton pump inhibitors (PPI) had a richer and more diverse microbiota composition than the PPI group [16]. A clinical study of patients with both cancer and depressive symptoms investigated the effects of *Xiao-Chai-Hu-Tang (XCHT)*. The study

showed that *XCHT* partially reversed gut dysbiosis, and that the gut microbiota mediated the inhibition of tumor progression by *XCHT* in patients with cancer [17]. A randomized controlled trial (RCT) of probiotics combined with the herbal medicine *Bofutsushosan* by Lee et al. [18] resulted from the trial registered in CRIS in 2012 [19]. This trial compared the effects of probiotics and a placebo while administering *Bangpungtongsungsan* to both the treatment and control groups. The levels of some gut microbiota were modified after probiotic administration, and particular species were correlated with body parameters such as body mass index (Table 1).

Table 1. Clinical trials reported on gut microbiome change with herbal medicine intervention

First author, year of publication	Patients	Treatment group vs. Control group (number)	Duration	Gut microbiome analysis	Results regarding gut microbiome
Yamashita, 2022 [14]	Obstructive jaundice (biliary drainage)	*Inchinkoto* (52)	4 days	16S rRNA gene sequence analysis	The stool genipin-producing activity was correlated with stool profile and the change of bile flow
Hanada, 2021 [15]	Colon cancer (laparoscopic colectomy)	*Daikenchuto* (8) vs. none (9)	4 wks	16S rRNA gene metagenome sequencing in fecal samples	The postoperative recovery of the concentration of fecal DNA: T > C
Zhang, 2021 [16]	Nonerosive reflux disease	*JianpiQinghua granules* plus (omeprazole (10mg) & dummy omeprazole (10mg)) or omeprazole (20mg) (93) vs. PPI (94)	6 wks (4: treatment, 2: none)	16S rRNA gene sequencing	Richness and diversity over the study period: T>C
Shao, 2021 [17]	Malignant tumor	*Xiao-Chai-Hu-Tang* (30) vs. Placebo (31)	6 wks	16S rRNA sequencing	*XCHT* ameliorates gut dysbiosis in cancer patients
Lee, 2014 [18]	Obesity	*Bofutsushosan herbal extracts* + Probiotics (DUOLAC7) (17) vs. Placebo (19)	8 wks	Gut microbiota composition	Levels of *B. breve*, *B. lactis*, *L. rhamnosus* were significantly increased ($p<0.05$)

T, treatment; C, control; PPI, proton pump inhibitor; wks, weeks; *B. breve*, *Bifidobacterium breve*; *B. lactis*, *Bifidobacterium lactis*; *L. rhamnosus*, *Lactobacillus rhamnosus*.

3.2 Clinical trials on herbal medicine analyzing gut microbiome registered in CRIS

Among the 25 clinical trials of the gut microbiome registered in the CRIS, herbal medicine was used as an intervention in 6 trials. All trials aimed to analyze the gut microbiome before and after administration of herbal medicine. The six trials consisted of five RCTs and one prospective observational study. The participants had obesity [19, 20], metabolic syndrome [18], [21], hangovers [22], and functional dyspepsia [23]. Sample sizes ranged from 10 to 120.

The observational study aimed to recruit patients diagnosed with functional dyspepsia and 'Dam-Eum' pattern and analyze the changes in the ratio of microorganisms for two weeks [23]. An RCT for metabolic syndrome used red ginseng capsules to compare the differences in intestinal microbial rates by 16s rRNA sequencing between the first and 57th administration days [21]. A clinical trial using *Hwangryunhaedok-tang (redoxin)* for hangovers aimed to identify changes in the gut microbiota before and after the administration of *redoxin* and placebo [22]. This RCT had a crossover design with a two-week washout period. A clinical trial

used the gut microbiome to assess constitution-specific drug response [24]. According to the Sasang constitutional medicine, the herbal medicines *Taeumjowee-tang*, *Yanggyuksanhwa-tang*, and *Palmulgunja-tang*, which were included in the trial, are normally used for Tae-eum, So-yang, and So-eum types, respectively [25]. In this trial, patients were diagnosed with the constitution, but they would have been prescribed herbal medicines regardless of the constitutional type to investigate drug metabolism in the constitution with the gut microbiome [25]. Another RCT on obese patients classified the constitution, and the single herbs *Ginseng*, *Rehmanniae radix*, and *Ephedrae herba*, which correspond to the So-eum, So-yang, and Tae-eum types, respectively, were distributed randomly, regardless of the constitution. The primary outcome was the difference in the gut microbiota ratio, with secondary outcomes, such as weight, body fat mass, and blood lipid profile [20]. A clinical trial using *Bangpungtongsungsan* with probiotics compared the number of gut microbes at the initial visit and week 8 as a secondary outcome [19] (Table 2).

Table 1. Summary of clinical trials enrolled in Clinical Research Information Service in Korea

Year	Study design	Patients	Sample size (T; C)	Treatment group (Control group)	Outcome measures	Current status
2020 [23]	Single-arm, prospective, observational	Functional dyspepsia	10	Herbal medicine (N/S)	The rate of change in the proportion of microorganisms	Recruiting
2020 [21]	RCT	Metabolic syndrome	60 (30; 30)	*Red ginseng capsule* 500mg*4 (Placebo 350mg*4) 3times/day*8wks	Differences in intestinal microbial rates through 16s rRNA sequencing	Active, not recruiting
2019 [22]	RCT	Hangover	40 (20; 20)	*Hwangryunhaedok-tang* (Redoxin capsule) 2 times (day 0, day 1) / wash out 14 days / placebo 2 times (day 14, day 15)	Change of gut microbiota	Recruiting
2014 [24]	RCT	Metabolic diseases/disorder	45 (15 for each group)	Group 1: *Taeumjowee-tang* Group 2: *Yanggyuksanhwa-tang* Group 3: *Palmulgunja-tang*	Difference of intestinal microbiota ratio (Phylum, genus, species, class, family, etc.)	Recruiting
2013 [20]	RCT	Obese	120 (40 for each group)	Herba extract granule Group 1: *Ginseng* Group 2: *Rehmanniae Radix* Group 3: *Ephedrae*	Difference of intestinal microbiota ratio	Completed
2012 [19]	RCT	Obese	40 (20, 20)	*Bangpungtongsungsan* + probiotics (*Bangpungtongsungsan* + placebo)	Number of intestinal microbiota	Completed

T, treatment group; C, control group; RCT, randomized controlled trial; N/S, not specified; wks, weeks.

4. Discussion

The present study showed that the number of previous studies analyzing changes in the gut microbiome following herbal medicine administration has recently increased. The clinical trials registered in Korea cover symptoms and diseases closely related to the GI tract, including functional dyspepsia, metabolic syndrome, obesity, and hangovers. Meanwhile, three out of five articles searched in MEDLINE were studies on cancer: obstructive jaundice associated with malignant tumors [14], patients who underwent laparoscopic colectomy following colon cancer [15], and cancer comorbid depressive symptoms [17]. A previous review of herbal medicine and the gut microbiota focusing on experimental studies also showed that the research topics were primarily GI diseases and metabolic syndrome [11]. Research on the microbiome and herbal medicines has focused on the effects of herbal medicines on various diseases, including cancer and GI diseases.

Most studies have used 16S rRNA sequencing to analyze the gut microbiome. This is presumably because 16S rRNA sequencing enables species-level identification and is less expensive than shotgun metagenomics [2]. Considering the specialized knowledge on metagenomics, high cost of gut microbiome research, and the need for prospective clinical studies with large sample sizes [26], it would be more efficient to conduct multicenter collaborations to study the gut microbiome for specific diseases rather than sporadic research by individual researchers.

A previous review on experimental studies suggested that herbal medicines affect the composition of the gut microbiota [11]. In this study, we analyzed recent clinical studies on herbal medicine and gut microbiota to determine the study design, types of herbal medicines used, methods of gut microbiota analysis, and primary results.

Dysbiosis is associated with a loss of response to immunotherapy [27]. Our review indicates that herbal medicines can contribute to the reversal of gut dysbiosis [17] and faster recovery of fecal DNA concentration after colon cancer surgery [15]. Considering the microbiome-modulating effects of herbal medicines, personalized integrative cancer therapy could be promising by combining immune checkpoint inhibitors and herbal medicines through microbiome analysis. Further clinical trials and real-world evidence on the gut microbiome of patients with cancer are required to determine the individual characteristics of patients with cancer and the efficacy of integrative cancer therapy combining herbal medicine and immune checkpoint inhibitors. Analysis of the gut microbiota should be prioritized when investigating individual characteristics of the human body.

Our study has several limitations. First, only the CRIS and MEDLINE databases were used to screen the existing literature. Second, specific changes in the gut microbiota were excluded from this study. Third, a small number of included studies showed limited characteristics and trends of current studies. Nevertheless, this review provides a quick overview of recent clinical trials on gut microbiota and herbal medicine, thus indicating future research topics. We expect that future cancer treatments will begin with the diagnosis and treatment of dysbiosis of the gut microbiome.

5. Conclusions

We analyzed the characteristics of recent clinical studies on gut microbiota and herbal medicine. Most studies have analyzed the number or ratio of gut microbiota before and after the administration of herbal medicine using 16S rRNA sequencing. Comparing the research topics of domestic trials and papers from MEDLINE, there is an urgent need for research on herbal medicine and gut microbiota in patients with cancer in Korea. Further clinical studies are needed to investigate the efficacy and safety of integrative cancer therapy combining immunotherapy and herbal medicine using gut microbiota analysis for precision medicine.

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Conflicts of Interest: The authors declare no conflict of interest.

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