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Review

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A comprehensive update: gastrointestinal microflora, gastric cancer and gastric premalignant condition, and intervention by traditional Chinese medicine

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Abstract: With the recent upsurge of studies in the field of microbiology, we have learned more about the complexity of the gastrointestinal microecosystem. More than 30 genera and 1000 species of gastrointestinal microflora have been found. The structure of the normal microflora is relatively stable, and is in an interdependent and restricted dynamic equilibrium with the body. In recent years, studies have shown that there is a potential relationship between gastrointestinal microflora imbalance and gastric cancer (GC) and precancerous lesions. So, restoring the balance of gastrointestinal microflora is of great significance. Moreover, intervention in gastric premalignant condition (GPC), also known as precancerous lesion of gastric cancer (PLGC), has been the focus of current clinical studies. The holistic view of traditional Chinese medicine (TCM) is consistent with the microecology concept, and oral TCM can play a two-way regulatory role directly with the microflora in the digestive tract, restoring the homeostasis of gastrointestinal microflora to prevent canceration. However, large gaps in knowledge remain to be addressed. This review aims to provide new ideas and a reference for clinical practice.

Key words: Gastric cancer (GC); Gastric premalignant condition (GPC); Precancerous lesion of gastric cancer (PLGC); Gastrointestinal microflora; Intervention by traditional Chinese medicine (TCM)

1 Introduction

Gastric cancer (GC) has become a global health threat because of its increasing morbidity and mortality (Yu and Baade, 2017; Global Burden of Disease Cancer Collaboration et al., 2019). In the pathologic evolution of GC, atrophy, intestinal metaplasia, pseudopyloric gland metaplasia, and dysplasia are regarded as gastric premalignant condition (GPC) or precancerous lesion of gastric cancer (PLGC) (Ge et al., 2019), which represent effective interventional stages to prevent GC. With the development of microecology, studies on GC and GPC have turned to the gastrointestinal microflora, and some progress has been made. Furthermore, the application of traditional Chinese medicine (TCM) has achieved good results in related clinical trials. In this paper, we briefly review the main composition and distribution of gastrointestinal microflora, the influencing factors, the relationship between gastrointestinal microflora and GC and GPC, and intervention by TCM in the prevention and treatment of gastric canceration, with the aim of providing a new perspective for better clinical service.

2 Overview of the gastrointestinal microflora

2.1 Main composition and distribution of the gastrointestinal microflora

There are more than 1000 species of microflora belonging to 30 genera in the body, and the total cell number is as high as 1×10^{14}, which is about 10 times the total number of human cells (Wang, 2015). Since the discovery and cultivation of *Helicobacter pylori*

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dispelled the traditional concept that the stomach is an "aseptic organ," a variety of species of gastric microflora have been found. They belong to five main phyla: Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, and Bacteroidetes. There are more than 100 genera, including *Lactobacillus*, *Streptococcus*, *Prevotella*, *Veillonella*, *Rothia*, *Haemophilus*, *Neisseria*, etc. (Ianiro et al., 2015). Different microflora colonizes different regions of the stomach, especially the gastric juice and gastric mucosa. Sung et al. (2016) found that while there is more microflora in the gastric mucosa, the species of microflora in gastric juice are more diverse. The microflora in the gastric mucosa is composed mainly of Firmicutes and Proteobacteria, while most of microflorae in gastric juice are Firmicutes, Actinobacteria, and Bacteroidetes. However, most of them are transient because of the strong acid characteristics of gastric juice (Bik et al., 2006; Wu et al., 2014; Nardone and Compare, 2015). In addition, some studies have reported that there are no substantial differences among the microflora from different parts of the gastric cavity (Delgado et al., 2013).

The intestinal microflora is also known as the "forgotten functional organ." There are about 500–1000 species of microflora living in the intestinal tract, of which more than 400 species can be cultured at present. They can be divided into dominant microflora and secondary microflora based on their abundance. Alternatively, they can be divided into probiotics, opportunistic pathogens, and pathogens according to their functions. The number of dominant microflora is more than 10 CFU/g (CFU, colony-forming unit). These generally consist of specific anaerobic microflora, including *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Clostridium*, and *Ruminococcus*, which can greatly affect the physiology of the body. Most of the secondary microflora is aerobic or facultative anaerobic microflora and transient flora, which may have potential pathogenicity, and usually consist of *Streptococcus*, *Escherichia coli*, and similar bacteria. In addition, the distribution of microflora is not alike in different regions of the intestine. For example, the structure of the microflora in the proximal small intestine is similar to that in the stomach, but also includes *E. coli*. The distal ileum contains mainly *E. coli* and a certain number of anaerobes, including *Bacteroides*, *Clostridium*, and *Bifidobacterium*. Furthermore, the number of microflora in the distal ileocecal valve is much higher, and about 10.11–10.12 CFU/mL of microflora reside in the colon, including *Faecalibacterium*, *Eubacterium*, and *Bifidobacterium*. Besides, the dominant microflora may be replaced following changes in the internal environment. Table 1 shows the main composition and distribution of gastrointestinal microflora.

2.2 Factors influencing gastrointestinal microecology

Because of differences among populations and samples, as well as detection methods, there are still many gaps in our knowledge of microflora, and the mechanism of the formation of the gastrointestinal microflora has not been fully elucidated. It is generally accepted that *H. pylori* infection, long-term use of antibiotics, proton pump inhibitors (PPIs), H2 receptor inhibitor (H2RI) or immunosuppressive agents, probiotics or vitamin supplements, diet or age, and location of patients can change the gastrointestinal microenvironment and affect the microflora (Espinoza et al., 2018) (Fig. 1).

Currently, the most controversial issue concerns the impact of *H. pylori*. Some researchers reported that an effect of *H. pylori* colonization on the gastrointestinal microflora was not obvious. Bik et al. (2006) proposed that there was no significant difference in the gastric

Table 1 Main composition and distribution of gastrointestinal microflora

Region	Main composition	Distribution
Gastric microflora	Phyla: Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, and Bacteroidetes; Genera: *Lactobacillus*, *Streptococcus*, *Prevotella*, *Veillonella*, *Rothia*, *Haemophilus*, *Neisseria*, etc.	Gastric mucosa: Firmicutes and Proteobacteria; Gastric juice: Firmicutes, Actinobacteria, Bacteroidetes, etc.; Passers-by
Intestinal microflora	Dominant microflora: specific anaerobic microflora, including *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Clostridium*, *Ruminococcus*, etc.; Secondary microflora: aerobic or facultative anaerobic microflora such as *Streptococcus*, *Escherichia coli*; Transient flora pathogens	Proximal small intestine: similar to the stomach (*E. coli*, etc.); Distal ileum: *E. coli* and anaerobes (*Bacteroides*, *Clostridium*, *Bifidobacterium*, etc.); Distal ileocecal valve: *Faecalibacterium*, *Eubacterium*, *Bifidobacterium*, etc.

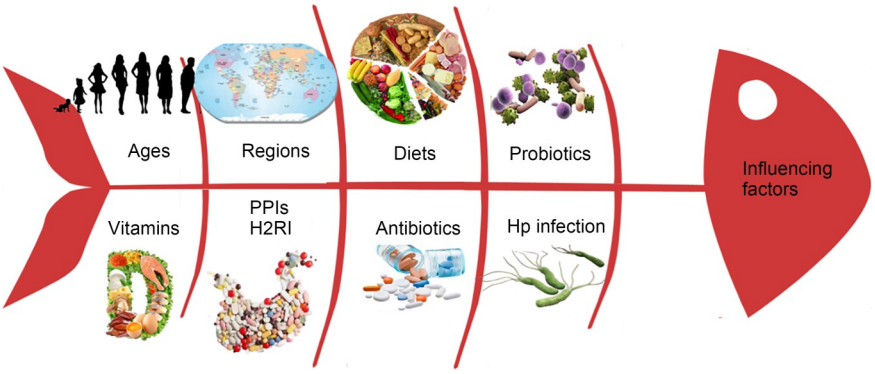

Fig. 1 Factors influencing gastrointestinal microecology. PPIs: proton pump inhibitors; H2RI: H2 receptor inhibitor; Hp: *Helicobacter pylori*.

microflora between *H. pylori*-positive and *H. pylori*-negative subjects based on the sequential detection of 16S ribosomal RNA (rRNA). After examining 215 samples, Khosravi et al. (2014) concluded that the ecological structure of gastrointestinal microflora was not affected by *H. pylori* infection. A recent study by Coker et al. (2018) on patients with chronic gastritis and intestinal metaplasia showed that the relationship between gastrointestinal microflorae in *H. pylori*-negative subjects was more intimate, while in general, there was no marked difference in the abundance or diversity of gastrointestinal microflora between those subjects affected by *H. pylori* and those not. However, a considerable number of researchers hold the opposite view. They believe that the colonization of *H. pylori* can change the gastrointestinal microenvironment such that conditions become suitable for some microflorae, but no longer suitable for survival of the original microflorae. Therefore, *H. pylori* infection has a great influence on the gastrointestinal microecology (Schulz et al., 2015). Andersson et al. (2008), using 454 pyrosequencing, reported that *H. pylori* infection can cause a striking change in the diversity of the gastric microflora. They found that the abundance of some microflorae such as those of the phyla Firmicutes, *Bacteroides*, and *Actinomycetes* decreased. Some microflorae even disappeared, including *Eubacterium cylindroides*, *Prevotella*, *Clostridium coccoides*, and *Clostridium ieptum*. In contrast, the abundance of some other microflorae increased, consisting mainly of Proteobacteria, Acidobacteria, *Spirillum*, and similar bacteria. Besides, in different subjects, the microflora of the same phylum comprises different species. For example, there are mainly γ-Proteobacteria and β-Proteobacteria in the digestive tracts of *H. pylori*-negative subjects, but ε-Proteobacteria in those of *H. pylori*-positive subjects (Brawner et al., 2017; Llorca et al., 2017).

In addition to *H. pylori*, some researchers have found that other *Spirillum* can affect gastrointestinal microecology. Peng et al. (2017) reported that co-infection of *H. pylori* with *Helicobacter suis* or *Helicobacter felis* can significantly reduce the infection rate of nitrite-producing bacteria. The mechanism may be related to acid inhibition. The long-term use of PPIs or H2RI can inhibit gastric acid secretion and affect the gastrointestinal microenvironment such that some microflora will overgrow (Tsuda et al., 2015). For instance, Jackson et al. (2016) suggested that the growth of *Clostridium* was inhibited while the growth of *Streptococcus* and *Lactobacillus* was promoted after the prolonged use of PPIs. In addition, the extensive use of antibiotics can inhibit the growth of sensitive bacteria, while the number of drug-resistant bacteria increases, resulting in an imbalance of gastrointestinal microecology in the long run. Furthermore, it has been reported that the diversity of gastrointestinal microecology increases after vitamin D_3 supplementation (Bashir et al., 2016). Another important influencing factor is interaction with the immune state of the body, which can involve co-regulation. In a state of immunosuppression, *Lactobacillus* will overgrow, while the abundance of *Prevotella* and *Clostridium* will decrease (von Rosenvinge et al., 2013).

3 Gastric microflora and GC and GPC

3.1 *H. pylori* and GC and GPC

In recent years, many studies have confirmed that there are significant differences in the gastric microflora

between patients with gastropathy and healthy individuals, including composition, quantity, and structure. An imbalance of gastric microflora can induce gastritis, gastric ulcers, or other gastric diseases, which plays a potential role in the process of GC and GPC (Sgambato et al., 2017).

H. pylori is a Gram-negative parasitic bacterium in the epidermis of the gastric mucosa, and has been the most studied gastric bacterium in the past 40 years. As an independent risk factor for the development of GC, about 1%–2% of positive patients will eventually develop GC. About 79% of GC patients have *H. pylori* infection according to the survey by Plummer et al. (2016).

H. pylori appears as a kind of helical bacillus under an optical microscope, with 4–6 sheathed flagella that can be seen under an electron microscope. It can be adsorbed onto the surface of the gastric mucosa by its special reticular structure, resulting in a chronic inflammatory reaction through a series of stimulations. *H. pylori* can inhibit immune function and acid secretion to weaken the barrier of the gastric mucosa (Samarth, 2017). Su and Guo (2014) reported that *H. pylori* infection promotes gastric mucosal immunosuppression in two ways, by inducing the upregulation of forkhead box protein P3-positive ($Foxp3^+$) regulatory T cells (Tregs), and transforming growth factor-β1 (TGF-β1), interleukin-10 (IL-10), and other factors. The reduction of acid secretion by gastric parietal cells may also be a pathogenic mechanism. Li et al. (2014) found that *H. pylori* can restrain the activity of some enzymes in parietal cells, such as H^+-K^+-adenosine triphosphatase (ATPase), to inhibit acid secretion. In addition to inducing chronic inflammation (Watanabe et al., 2015), *H. pylori* can produce a variety of cytotoxic factors, including cytotoxin-associated gene A (Cag A), vacuolating cytotoxin A (Vac A), and outer membrane proteins (OMPs) (Chmiela and Gonciarz, 2017), which can promote the occurrence or development of GC and GPC directly or indirectly. The relationship between Cag A and GC has always been controversial, and focused mainly on studies of various signaling pathways. Progress has been made in genomics in recent years. Saeki et al. (2013) found that Cag A causes inflammation mainly through affecting the nuclear factor-κB (NF-κB) signal pathway and inhibiting the activity of Caspase-8 and the expression of tumor protein p53 (TP53), resulting in abnormal cell morphology (Blaser and Atherton, 2004). Vac A can repress T lymphocytes and macrophages, and activate vascular endothelial growth factors (VEGFs) to cause gastric mucosal ulcers (Meng et al., 2018; El-Shouny et al., 2020).

Eradication of *H. pylori* to prevent GC has achieved global consensus, which can effectively reduce the recurrence and mortality rate of GC within three years (Bae et al., 2014). At present, the consensus recommendation for treatment is a quadruple regimen of PPI, two antibiotics, and bismuth. This can effectively improve the inflammatory response and acid secretion, and restore the microecological environment of the stomach to prevent injury to the gastric mucosa. For instance, according to the investigation of follow-up by Ma et al. (2012), the incidence of GC in patients that received *H. pylori* eradication therapy decreased significantly after 15 years. However, some studies reported that the eradication of *H. pylori* cannot completely prevent the production of GC. For example, a meta-analysis by Rokkas et al. (2017) showed that *H. pylori* eradication therapy is not effective in the treatment of GC for patients with intestinal metaplasia or dysplasia. A seven-year follow-up survey by Wong et al. (2004) suggested that in GC patients with *H. pylori* infection there was no statistical difference whether they received eradication therapy or not. Some studies even found that the incidence of other digestive diseases such as gastroesophageal reflux and esophageal cancer increased with the eradication of *H. pylori* (Venerito et al., 2016). Besides, although about 50% of the world's people have been infected with *H. pylori*, some have suffered no discomfort.

These mixed conclusions suggest that people need to reconsider the relationship between *H. pylori* and the host. On the one hand, the colonization of *H. pylori* can change the protogastric microecology, cause an increase in other potentially carcinogenic microflora (Jo et al., 2016), and have a long-term impact on the gastric microenvironment. On the other hand, some researchers think that both the abnormal colonization and eradication of *H. pylori* can affect the gastric microecology balance, and it is necessary to minimize the destruction of homeostasis in the internal environment during intervention therapy (Yap et al., 2016; Li et al., 2017).

3.2 Other gastric microflora and GC and GPC

It has been recognized that *H. pylori* infection plays an important role in the development of GC and

GPC. In past studies, people paid too much attention to *H. pylori*, which led to the neglect of the relationship between the colonization of other gastric microflora and carcinogenesis. For instance, some studies reported that non-*H. pylori Helicobacters* (NHPHs) are also associated with GC and GPC. More than 30 species of NHPHs have been cultured from the stomach, including *H. suis*, *H. felis*, *Helicobacter salomonis*, and *Helicobacter bizzozeronii* (Peng et al., 2017). About 12% of the patients have co-infection of *H. pylori* and NHPHs (Liu et al., 2015).

In addition to *H. pylori* and NHPHs, other changes in gastric microflora can lead to GC. A survey by Eun et al. (2014) showed that the abundance and diversity of gastric microflora in patients with GC were increased compared with those in patients with gastritis and metaplasia, especially *Streptococcus* species, which are related to he susceptibility of patients (Engstrand and Lindberg, 2013; Dong et al., 2017). Figueiredo et al. (2013) found that the changes of gastric microflora in patients with GC were characterized by an increase of *Proteus*, and a decrease of *Bacteroides* and *Fusobacterium*. Aviles-Jimenez et al. (2014) detected the gastric microflora in patients with non-atrophic gastritis, intestinal metaplasia, and GC. They found that with the development of the disease, the numbers of *Neisseria*, *Porphyromonas*, and *Streptococcus* species decreased, while the numbers of *Lachnospira*, *Lactobacillus*, *Prevotella*, and *Veillonell* species increased (Sohn et al., 2017). What's more, the gastric microflora of patients with atrophic gastritis has a tendency to change from *Prevotella* to *Streptococcus* (Engstrand and Lindberg, 2013). It has also been reported that, compared with patients with non-atrophic gastritis, there is no marked difference in the species of gastric microflora in patients with atrophic gastritis, but the number is significantly increased, especially the *Prevotella* species (Dong et al., 2017). In addition, the content of nitrite in the gastric juice of patients with GC is higher than that of healthy people whether they are infected with *H. pylori* or not. Jo et al. (2016) found that the content of nitrate-reducing bacteria (NB), including *Staphylococcus*, *Haemophilus*, *Veillonella*, *Clostridium*, *Nitrospira*, *Lactobacillus*, and *E. coli* in GC patients who were not infected with *H. pylori*, was about twice as high as that in a control group (Herrera and Parsonnet, 2009). Yu et al. (2017) also found that the amount of NB, such as *Lachnospira*, *Lactobacillus*, *E. coli*, and *Burkholderia*, in GC patients with *H. pylori* infection was significantly greater than that in a control group. Researchers speculated that these changes in the gastric microflora can promote the accumulation of nitrite in the stomach (Shiotani et al., 2004), linking to cancer by stimulating inflammation, proliferation of cells, and production of some metabolites (Abreu and Peek, 2014). *H. pylori* and other gastric microflora not only act independently, but also influence each other to induce the development of GC and GPC. Fig. 2 shows the relationship between gastric microflora and GC and GPC.

4 Intestinal microflora and GC and GPC

4.1 Research status of intestinal microflora and GC and GPC

Early studies on microecology and GC and GPC focused on gastric microflora, but recently, more and more researchers have begun to pay attention to intestinal microflora. They confirmed that an abnormal intestinal microflora may be one of the causes of GC, and prevention and treatment of GC cannot be separated from the role of intestinal microflora. Some studies even suggested that the association between gastrointestinal symptoms and the duodenal microflora may be even stronger in some patients than the association with the gastric microflora (Gong, 2019; Zheng, 2019).

There are significant differences in the duodenal microflora between normal subjects and patients with gastrointestinal metaplasia, especially *H. pylori*-negative patients. It has been suggested that an imbalance of the duodenal microflora is related to gastrointestinal metaplasia. Some studies found that the richness and diversity of intestinal microflora changed significantly during the development from non-atrophic gastritis to GC and GPC (Dias-Jácome et al., 2016; Ferreira et al., 2018). The numbers of *Streptococcus*, *Haemophilus*, *Neisseria*, *Prevolla*, *Porphyromonas*, and similar bacteria decreased significantly, while the numbers of *Lactobacillus*, *Enterococcus*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and similar bacteria increased. Gao et al. (2011) extracted and analyzed the composition of the intestinal microflora of 42 patients with GC, and found some differences compared to the intestinal microflora of normal subjects. However, no characteristic changes in the microflora structure related to GC

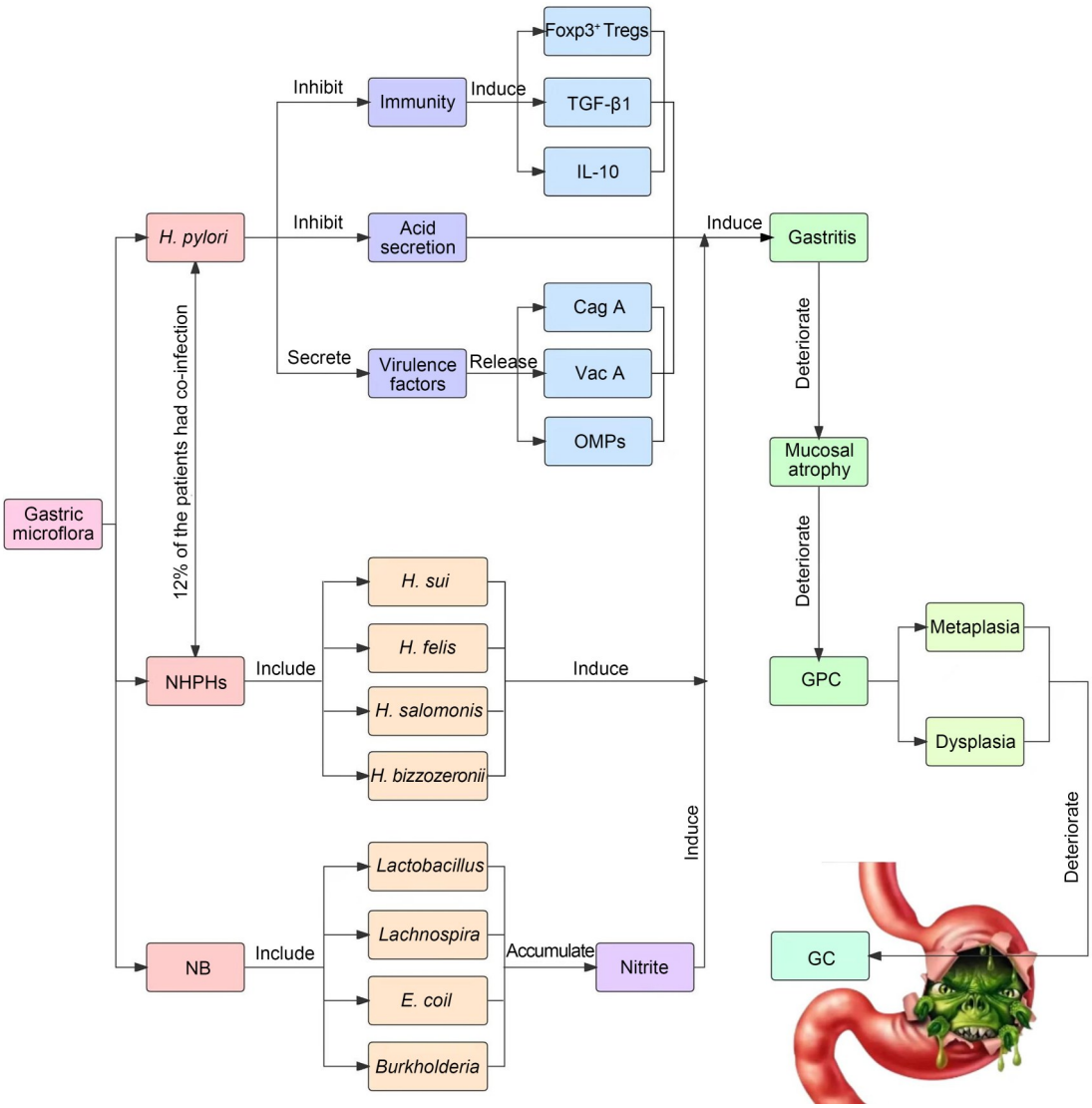

Fig. 2 Relationship between gastric microflora and GC and GPC. GC: gastric cancer; GPC: gastric premalignant condition; *H. pylori*: *Helicobacter pylori*; *H. sui*: *Helicobacter sui*; *H. felis*: *Helicobacter felis*; *H. salomonis*: *Helicobacter salomonis*; *H. bizzozeronii*: *Helicobacter bizzozeronii*; *E. coli*: *Escherichia coli*; NHPHs: *non-H. pylori Helicobacters*; NB: nitrate-reducing bacteria; TGF-β1: transforming growth factor-β1; IL-10: interleukin-10; OMPs: outer membrane proteins; Tregs: regulatory T cells; Cag A: cytotoxin-associated gene A; Vac A: vacuolating cytotoxin A; Foxp3⁺: forkhead box protein P3-positive.

were reported. Zhu et al. (2017) compared the structure of the intestinal microflora between seven patients with GC and three healthy controls, and found that the numbers and species of intestinal probiotics, including *Eubacterium rectale*, *Clostridium leptum*, *Dorealongicatena*, and similar bacteria, were lower in patients with GC. In contrast, the opportunistic pathogens increased, including *E. coli*, *Streptococcus salivarius* subsp., *Lactobacillus salivarius*, and similar bacteria. Furthermore, the number of *Lactobacillus mucosae* increased in two patients. Table 2 shows the gastrointestinal microflora associated with GC and GPC.

4.2 Mechanism of the effect of intestinal microflora on GC and GPC

4.2.1 Cancer-promoting mechanism of intestinal microflora imbalance

4.2.1.1 Releasing cytotoxins and related metabolites

Current studies have confirmed that when the intestinal microflora is imbalanced, a large number of cytotoxins released by pathogenic bacteria can induce inflammation, damage gastrointestinal mucosal cells, and promote the production of cancer. For example,

Table 2 Gastrointestinal microflora associated with GC and GPC

Region	Species
Gastric microflora	*Helicobacter pylori*; NHPHs: *Helicobacter sui*, *Helicobacter felis*, *Helicobacter salomonis*, *Helicobacter bizzozeronii*, etc.; NB: *Lachnospira*, *Lactobacillus*, *Escherichia coli*, *Burkholderia*, *Staphylococcus*, *Haemophilus*, *Veillonella*, *Clostridium*, *Nitrospira*, etc.
Intestinal microflora	Firmicutes: *Streptococcus*, *Lactobacillus*, *Enterococcus*, *Eubacterium rectale*, *Clostridium leptum* group, *Dorealongicatena*, *Streptococcus salivarius* subsp., *Lactobacillus salivarius*, etc.; Proteobacteria: *E. coli*, *Haemophilus*, *Neisseria*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, etc.; Bacteroidetes: *Prevolla*, *Porphyromonas*, etc.

GC: gastric cancer; GPC: gastric premalignant condition; NHPHs: non-*H. pylori Helicobacters*; NB: nitrate-reducing bacteria.

Enterococcus faecalis can release reactive oxygen species and superoxides. Variation in the internal environment can change *E. coli* from a symbiotic bacterium to a pathogen (Shen et al., 2014), releasing cytotoxins such as colicin, leading to DNA damage (Wong et al., 2019). Besides, it is also one of the main drug-resistant bacteria among Gram-negative bacteria (Landy et al., 2015), and some Gram-negative bacteria can produce cytolethal distending toxins (Shirokawa et al., 2014). *S. salivarius* subsp. and *L. salivarius* also can cause bacteremia (Wang et al., 2016a, 2016b). *Lactobacillus* are usually considered probiotic, but they can induce some serious infections when the body is immunocompromised (Salminen et al., 2004).

In addition to promoting cancer directly by secreting cytotoxins, related metabolites such as bile acids (Jia et al., 2019), polyamines, and specific enzymes released by the intestinal microflora can promote the production of GC and GPC. Bile acids can induce the canceration of gastric epithelial cells through extracellular signal-regulated kinase (ERK), the Janus kinase-signal transducer and activator of transcription-3 (JAK-STAT3), and other signaling pathways (Wan et al., 2020). Polyamines are necessary for maintaining the growth of the body, but excessive secretion may cause immune imbalance, induce the growth of cancer cells, and aggravate the imbalance of the gastrointestinal microflora, resulting in a vicious circle that induces GC (Johnson et al., 2015).

4.2.1.2 Damaging the immune system

Studies have shown that the intestinal microflora plays an important role in the formation of innate and adaptive immunity. An imbalance of the intestinal microflora will significantly inhibit the anti-tumor function of the gastrointestinal immune system (Palm et al., 2015). For instance, compared with normal mice, the lymphoid system in the intestinal mucosal barrier of aseptic mice was unsound, and the numbers and sizes of mesenteric lymph nodes, Peyer's patches, and intraepithelial lymphocytes (IELs) in the small intestine were insufficient. The adaptive immune function of the aseptic mice was inhibited simultaneously (Noverr and Huffnagle, 2004; Mazmanian et al., 2005; Rodríguez-Hernández et al., 2020). The amounts of T lymphocytes, B lymphocytes, and immunoglobulin A (IgA) decreased, as well as $CD4^+$ T lymphocytes in the spleen. All of these results suggest that the intestinal microflora is essential for the formation of the immune system.

An imbalance of the intestinal microflora affects not only the formation of the immune system, but also its functional expression. For example, the amount of IL-17 secreted by T helper 17 (Th17) in the intestinal tract of aseptic mice is relatively insufficient (Ivanov et al., 2008), because the production of Th17 requires adenosine triphosphate (ATP) provided by the metabolism of intestinal microflora (Atarashi et al., 2008). An imbalance of the intestinal microflora can also promote the expression of Toll-like receptors (TLRs) or nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and the secretion of inflammatory chemokines such as CCL5 and interleukins such as IL-6 and IL-8 (Shi et al., 2017). This induces inflammation and inhibits cell apoptosis, thus leading to GC and GPC.

4.2.1.3 Indirect carcinogenic effect

In addition to inducing GC and GPC directly, an imbalance of the intestinal microflora can also promote cancer indirectly by participating in metabolism or ectopic colonization. For instance, with the transformation of some specific bacteria in the intestinal microflora, bile acid is converted into deoxycholic acid (Alexander et al., 2017), alcohol is resolved into acetaldehyde (Arkan, 2017), and protein is broken down into nitrosamines and sulfides (Tsilimigras et al., 2017). All of these changes have carcinogenic effects on cells.

Furthermore, the pH of the stomach is increased by *H. pylori* infection (He et al., 2011; Zhao et al., 2013; Sultana et al., 2018), which results in changes of microbial composition and creates conditions for ectopic colonization of intestinal microflora. According to the study of Lertpiriyapong et al. (2014), ectopic colonization combined with *H. pylori* infection can promote the expression of oncogenes and TGF-β, increasing the risk of GC and GPC. Fig. 3 shows the relationship between the intestinal microflora and GC and GPC.

4.2.2 Cancer-preventing mechanism of intestinal probiotics

4.2.2.1 Direct inhibition of the formation of cancer cells

The production of GC is related to the activation of intracellular oncogenes and enzymes, including receptor protein tyrosine kinase (RPTK), mitogen-activated protein kinase (MAPK), and ERK (Caunt et al., 2015). Current studies have confirmed that the intestinal microflora plays a role in the prevention of GC and GPC, and intestinal probiotics and related metabolites can inhibit cancer cells (Saber et al., 2017). For instance, *Saccharomyces boulardii* can interfere with MAPK to inhibit the proliferation of cancer cells. *Lactobacillus casei* can promote apoptosis of cancer cells through stress-activated protein kinase (SAPK). Malfertheiner et al. (2012) found that *Lactobacillus* can restrain the GC cells and induce apoptosis. *Lactococcus* also has toxic effects on cancer cells.

What's more, dietary fibre metabolized by intestinal microflora can decompose into short-chain fatty acids (SCFAs), such as acetic acid, propionic acid, and butyric acid. SCFAs can regulate the pH in the colon to balance the intestinal microflora (Musso et al., 2011), and participate in oxidation, lipid synthesis, and energy metabolism (Wong et al., 2006) as nutritional sources (Samuel et al., 2008). SCFAs can also activate the death-associated protein kinase 1/2 (DAPK1/2) (Sivaprakasam et al., 2016), *p21* gene, and similar signaling pathways to achieve tumor inhibition (Bultman, 2014; Zitvogel et al., 2017). Furthermore, with the catabolism of intestinal microflora, ursodeoxycholic acid (UDCA) can induce autophagy and apoptosis to inhibit the development of GC and GPC (Zeng et al., 2019; Wan et al., 2020).

4.2.2.2 Positive regulation of the immune system

Damage to the immune system can also cause carcinogenesis, while intestinal probiotics can regulate inflammation (Fung et al., 2012; Zhang et al., 2020), including activating and promoting immunocytes such as dendritic cells, natural killer cells, and T helper cells (Morrison, 2012; Cai et al., 2016), and reduce the incidence of GC and GPC by re-organizing the immune system. Zhan et al. (2013) found that both the severities of inflammation and canceration were more serious in aseptic mice than in normal mice, confirming that the intestinal microflora is necessary for the immune system to exert an anti-cancer function. Nakamoto et al. (2017) reported that *Lactobacillus* can activate TGF-β1, promote regulatory dendritic cells to mature and secrete 1L-10, and activate intestinal lamina propria lymphocytes to secrete 1L-22, to inhibit inflammation and protect the gastric mucosal barrier. Segmented filamentous bacteria (SFB) can activate Th17 cells to release 1L-17 and 1L-22, and promote the secretion of β-defensin and mucus to protect the gastrointestinal mucosa (Gaffen et al., 2014). *Eubacterium*, *Clostridium*, and *Rothia* can produce butyrate, an important anti-tumor and anti-inflammatory factor (Kolho et al., 2015). Butyrate can inhibit the inflammatory response by inhibiting the NF-κB signaling pathway, promoting the differentiation of regulatory T cells, and reducing the release of inflammatory factors (Arpaia et al., 2013; Smith et al., 2013; Song et al., 2020). *C. leptum* can resist inflammation or pathogens to maintain the homeostasis of the internal environment (Landy et al., 2015). Fig. 4 shows how intestinal probiotics protect the mucosal barrier by regulating immunity.

4.2.2.3 Indirect anticarcinogenic effects

The intestinal microflora can improve pharmacological activity and reduce toxicity by participating in metabolism. Deng et al. (2008) reported that the intestinal microflora can reduce the toxicity of hydrazine in rats. Shen et al. (2014) speculated that the intestinal microflora might play an anticancer role by interfering with some signaling pathways. In addition, the duodenal microflora may induce gastrointestinal metaplasia and promote GC and GPC.

5 Research progress on treatment of GC and GPC by regulating the gastrointestinal microflora with TCM

There are no specific names for GC or GPC in TCM. They are commonly classified as tightness, nausea and vomiting, heartburn, and epigastric pain, or words

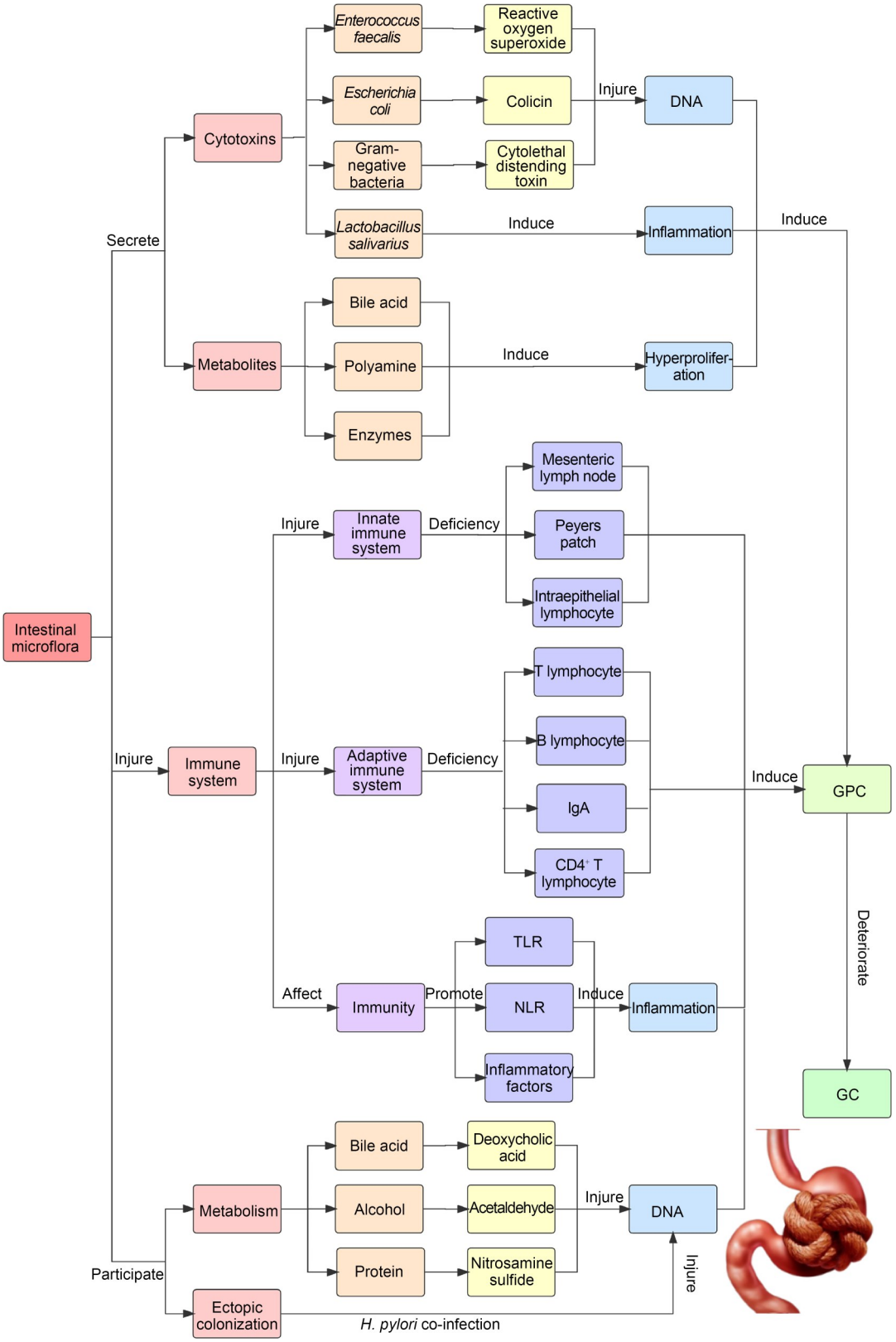

Fig. 3 Relationship between intestinal microflora and GC and GPC. GC: gastric cancer; GPC: gastric premalignant condition; IgA: immunoglobulin A; TLR: Toll-like receptor; NLR: nucleotide-binding oligomerization domain (NOD)-like receptor; *H. pylori*: *Helicobacter pylori*.

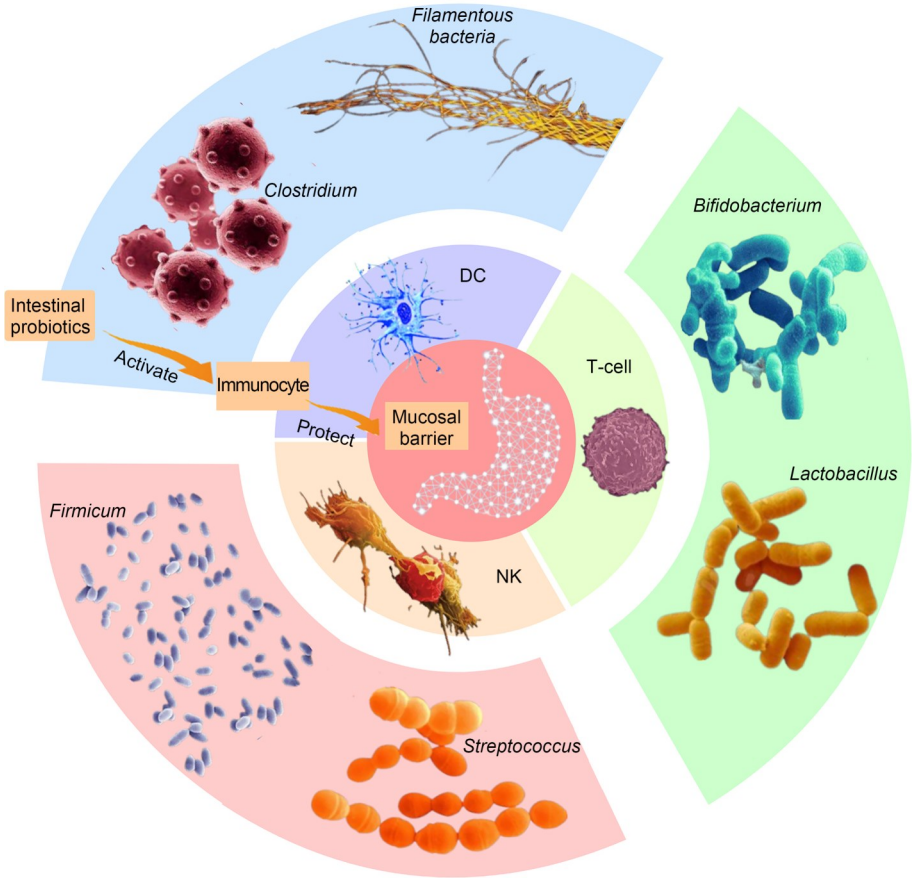

Fig. 4 Intestinal probiotics protect the mucosal barrier by regulating immunity. DC: dendritic cells; NK: natural killer cell.

to that effect, according to the symptoms. The concept of treatment based on syndrome differentiation and integrity is a hallmark of TCM, and emphasizes the dynamic balance of the body. The unity of the internal and external environment with biology is the core concept of microecology, and the high similarity of these concepts defines the interdisciplinary status. The composition of TCM is complex, as is the diversity of the species of microflora. Oral administration is the norm, and when a TCM enters the digestive tract, it can regulate the gastrointestinal microenvironment and maintain the balance of microflora by increasing the number and activity of probiotics, inhibiting pathogens, and preventing bacterial translocation. Conversely, the gastrointestinal microflora can promote the transformation and metabolism of TCM components (Fig. 5). More and more scholars are now proposing to combine microecology with TCM in clinical practice. It has been more than 30 years since the subject of "microecology of TCM" was put forward (Cai, 2019). Professor WEI, one of the founders of Chinese microecology, once predicted: "Microecology is likely to be a golden key to open the door of the mysteries of TCM" (Wei, 1989). The Japanese researchers, Kobayashi (1995) proposed that the intestinal microflora participate and increase the efficacy of Chinese herbal medicine following oral intake, and named this subject area "serum pharmacology." The development and improvement of such theories (Yue et al., 2019; Song et al., 2020) bring a lot of enlightenment to clinical practice.

However, the standard therapy for eradication of *H. pylori* is at present faced with dilemmas such as antibiotics abuse and increasing drug resistance. In response to these difficulties, the combination of TCM and Western medicine has achieved satisfactory results. Studies have shown that some TCMs and their active extracts can play an important role in eradicating *H. pylori*. *Coptis chinensis* and its extracts such as berberine and coptisine (Graham and Dore, 2016) are confirmed to have strong antibacterial characteristics. Berberine can reduce the cytotoxicity and proliferation of *H. pylori* (Chang et al., 2011), and coptisine has

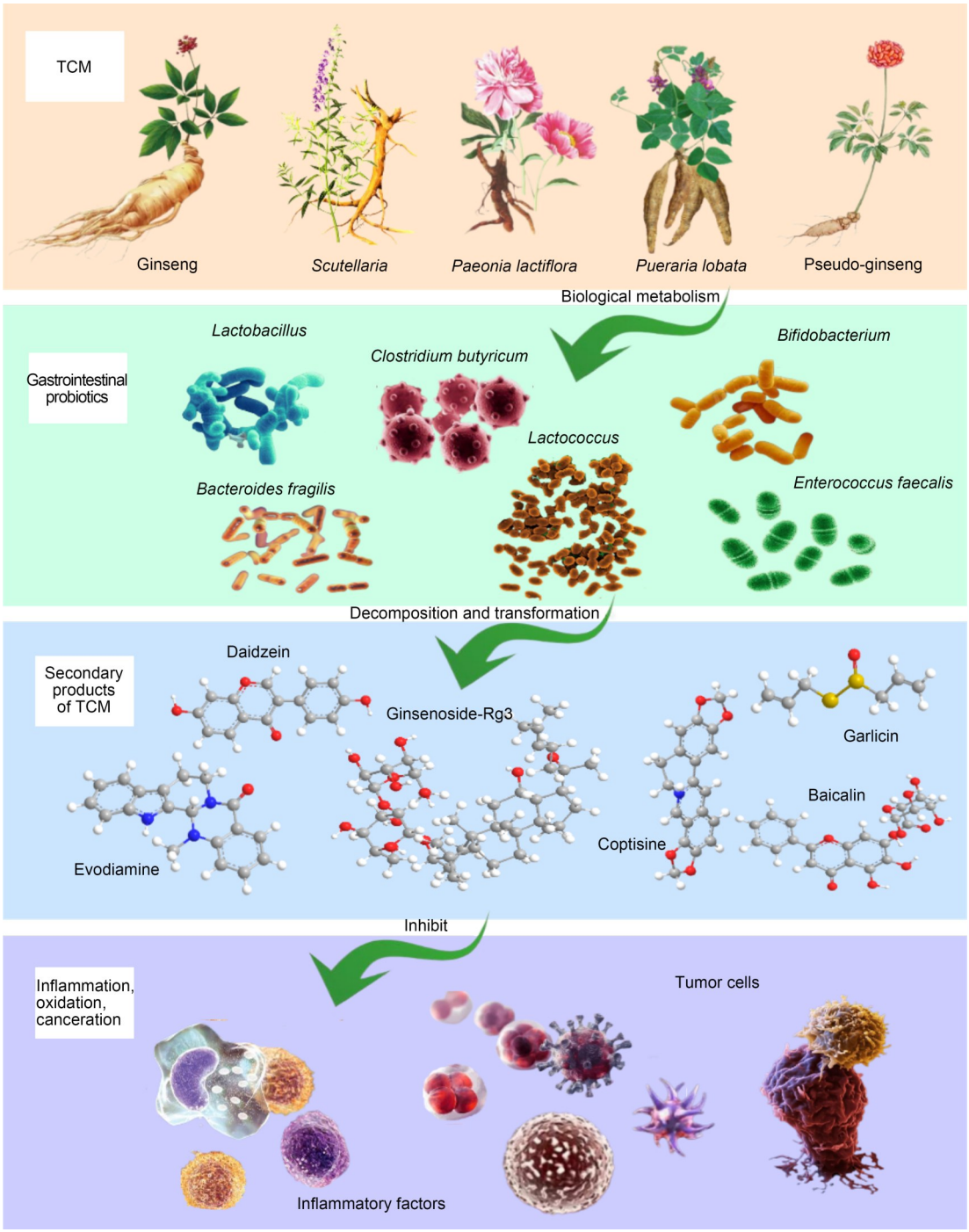

Fig. 5 Improving the efficacy of traditional Chinese medicine (TCM) through the metabolism of the gastrointestinal microflora.

anti-inflammatory and antimicrobial effects. Patchouli alcohol can reduce the activity of *H. pylori* by inhibiting urease gene expression (Lian et al., 2017). Other constituents, such as *Scutellaria baicalensis*, *Evodia* alkaloid and allicin, have certain antibacterial activity against *H. pylori* (He et al., 2020; Wang LL et al., 2020).

TCM generally takes a holistic approach: studies of monotherapy research can provide a reference, while clinical prescriptions are commonly TCM compounds combined with Western medicine, targeting the treatment of differentiated syndromes. Yang (2020) used a combination of TCMs in the “Huangqi Jianzhong

decoction" (composed of *Astragalus membranaceus*, *Cassia* twig, *Radix paeoniae* alba, ginger, prepared *Radix glycyrrhizae*, *Fructus ziziphi jujubae*, and maltose) for the treatment of patients infected with *H. pylori*, and found that the total effective rate of the treatment group was 95.6%, significantly higher than that of the control group. Li et al. (2016) observed that following the treatment with the "Xiangsha Liujunzi decoction" (composed of ginseng, *Atractylodes macrocephala*, *Poria cocos*, *Pinellia ternata*, dried tangerine peel, *Agastache rugosa*, licorice, and *Amomum villosum*), the eradication rate of *H. pylori* in the treatment group was 91.7%, which was significantly better than that of the control group. A variety of proprietary Chinese medicines or TCM decoctions combined with Western medicine have also achieved satisfactory clinical results.

According to recent studies, once pathological changes in the gastric mucosa develop to the stage of intestinal metaplasia or dysplasia, even the eradication of *H. pylori* cannot reduce the risk of GC (Jo et al., 2016). TCMs such as *Salvia miltiorrhiza* Bge and *Radix curcumae* have beneficial effects in patients with intestinal metaplasia or dysplasia, and might even reverse the mucosal pathology to some extent (Wu, 2002; Dai et al., 2017). Many other TCMs, including *Astragalus mongholicus*, *A. macrocephala*, *C. chinensis*, and *Sophora flavescens*, have been shown to have satisfactory effects. Modern pharmacological studies shown that they are rich in multiple active constituents, such as flavonoids, polysaccharides, and alkaloids, which can promote the degradation of the effective components of TCM to increase the absorption rate by balancing the microflora (Chen et al., 2018; Feng et al., 2018). This can improve the precancerous state and play an intervention role in the development of GC and GPC. Our group has been committed to the study of various chronic digestive system diseases for more than 30 years, and has accumulated systematic experience in the intervention of TCM in GPC. Weizhuan'an (composed of ginseng, roasted *Astragalus*, fried *A. macrocephala*, *S. miltiorrhiza*, zedoary, peach kernel, magnolia, *Polygonum cuspidatum*, ginger pinellia, and *P. ternata*) developed by our group for patients with GPC has been proved to reduce the clinical symptoms of patients effectively and improve mucosal pathology to some extent. The comprehensive effective rate is 89.58% after taking a course of treatment (Jiang et al., 2005; Yang et al., 2016; Meng et al., 2020). Based on recent studies, we aim to provide some references for clinical treatment.

TCMs entering the gastrointestinal tract orally cannot be completely absorbed directly, and the components of TCM that remain for a long time will go through the biological metabolism of the gastrointestinal microflora and related enzymes. The secondary products can then be used by the body, which improves the bioavailability of TCM effectively and enhances its anti-inflammation and anti-tumor roles. For example, Wang et al. (2016a, 2016b) found that ginsenosides Rg3 and Rh1 from ginseng transformed by the intestinal microflora can reduce hazardous compounds containing 2-hydroxybutyric acid or malic acid, and inflammatory factors, while increasing linolenic acid and restoring the microflora structure. Moreover, Wang et al. (2016a, 2016b) found that pseudo-ginseng produced active metabolites such as notoginsenosides Rg1, Rg3, Rb1, and Rh1 by the transformation of intestinal microflora, which improved its efficacy. In addition, Xu et al. (2017) reported that paeoniflorin was more powerful when decomposed into paeoniflorgenin by the metabolism of β-glucosidase and esterase. *Lactobacillus brevis* and *Bacteroides fragilis* can catalyze paeoniflorin into active substances such as paeoniflorgenin and paeoniflorin, thereby improving efficacy. Flavonoids, polysaccharides, and alkaloids in TCM can also be metabolized by gastrointestinal microflora to improve pharmacological activity and reduce side effects. For example, *Bifidobacterium* and *E. faecalis* can convert puerarin into daidzein (Braune and Blaut, 2016). *Clostridium butyricum* and *B. fragilis* can decompose aconitine into lipoaconitine by metabolism. The anti-inflammatory, antioxidant, and anti-tumor activity of Curcumin (Zam, 2018), baicalin (Wang et al., 2015), and similar TCM compounds (Chen et al., 2017; Su et al., 2018; Wang J et al., 2020) can be significantly enhanced following transformation by gastrointestinal microflora.

6 Perspectives

For chronic inflammation to deteriorate to GC and GPC is a long-term process involving multiple factors and steps. Many gastrointestinal microflorae settled in the body play a role in promoting digestion and absorption, maintaining the physiological function of the digestive system. The development of molecular

detection technology and biological analysis has broadened our cognition of gastrointestinal microflora, and the pathological mechanisms of GC and other gastric diseases have been reconsidered. With the deepening of research, we have found that there is a relationship between the gastrointestinal microflora and GC and GPC. TCM has bidirectional regulatory effects on the gastrointestinal microflora, which is effective in the prevention of canceration. However, there are some deficiencies in our current knowledge.

First, the gastrointestinal microflora is characterized by numerous and complicated components, and affected by multiple factors such as differences in patients, investigation methods and sample sizes, and detection and analysis technologies. The specific microflora related to GC and GPC and their mode of action have not been fully clarified. Moreover, not all of the microflora detected are associated with GC and GPC. For example, researchers have confirmed that *Lactobacillus* in the gastric mucosa cannot affect the colonization of *H. pylori* or intervene in the development of chronic gastritis (Liu et al., 2015). In addition, many studies have shown that *H. pylori* infection is not completely related to GC. Therefore, more interventional studies are needed to explore the relationship between the gastrointestinal microflora and GC and GPC. Besides, most investigations have explored the gastric microflora, especially *H. pylori*, while there have been few reports on intestinal microflora, which can be a new area for in-depth study.

Second, although there is quite a lot of evidence that combinations of TCMs can enhance their role in preventing or treating GC and GPC, current experiments on the regulation of gastrointestinal microflora by TCMs are insufficient, and the mechanisms of interaction between them are still undefined. There is also a lack of in-depth research on the signaling pathways and specific targets regulated by TCM. Therefore, it is necessary to screen for the microflora which plays a critical role, clarify the interaction between the microflora and disease in follow-up studies, and establish a clear molecular mechanism and gene network, so as to provide a theoretical basis for microbial targeted therapy of TCM in clinical trials.

Last, but not least, the eradication of certain bacteria can bring a short-term curative effect, but can also cause a damaging overall imbalance. Therefore, we should consider the gastrointestinal microflora as part of the human microecosystem, and try to restore the balance between the body and the microecosystem from the perspective of "symbiosis." This may be a better strategy in the long term. To sum up, great progress has been made in recent studies, but research is in the initial stages and some knowledge gaps are waiting to be filled. How can the role of TCM in prevention and treatment be optimized with the assistance of microecology? This is the question we need to explore in the future.

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Author contributions

Yuting LU and Huayi LIU were responsible for conceptualization, article writing, and manuscript revision; Yuting LU, Kuo YANG, Yijia MAO, Lingkai MENG, and Liu YANG for picture design; Guangze OUYANG and Wenjie LIU for supervision and revision. All authors have read and approved the final manuscript, and therefore, take responsibility for the integrity of the study.

Compliance with ethics guidelines

Yuting LU, Huayi LIU, Kuo YANG, Yijia MAO, Lingkai MENG, Liu YANG, Guangze OUYANG, and Wenjie LIU declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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