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Review Article

Overview of research on the application of medicine food homologous bioactive ingredients to functional constipation

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Abstract: Medicine food homology (MFH) items are plants or foods that possess therapeutic characteristics and can be utilized as ingredients in food. In different cultures, people often use a variety of herbs, foods and plants to maintain good health. These homologues are considered to have potential pharmacological activities and are particularly important for the maintenance of gastrointestinal health. Functional constipation is a prevalent gastrointestinal disorder. The patients show symptoms such as difficulty in defecation, constipation and dry stool, which seriously affect the quality of life. Traditional treatments include lifestyle changes, dietary fiber supplementation and medication. Nevertheless, prolonged utilization of the medication might result in adverse reactions, and there are specific constraints in the management of functional constipation. Consequently, individuals are increasingly focusing on the homologous substances found in natural medicine that are also present in food and medicine, with the aim of discovering novel therapeutic approaches. In this paper, the research on functional constipation with drug and food homologous substances will be summarized, focusing on their role in promoting intestinal peristalsis, regulating intestinal flora, increasing fecal water and so on, so as to provide more effective treatment options for patients with functional constipation.

Keywords: bioactive ingredients; medicine food homology; constipation; functional constipation; mechanism of action

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1 Introduction

Medicine food homology (MFH) substances refer to natural compounds with both drug properties and food sources, which have significant effects on the treatment and maintenance of functional constipation (FC) due to their natural safety and effectiveness. The perspective of medicine and food homology aligns with the nutritional needs of individuals seeking a return to a natural, environmentally friendly, and health-conscious lifestyle. Due to the implementation of the "health China" strategy and the increasing health consciousness among the population, there is a growing interest in health products that use pharmaceutical and food homologous substances as ingredients. Consequently, the development of safe, healthy, and environmentally friendly health products is expected to have promising prospects[1]. FC is the predominant kind of long-term constipation. The prevalence of FC is increasing as a result of changes in diet structure, a faster pace of life, and social psychological variables. Furthermore, the pathophysiology of the disease is intricate, the disease progresses over a lengthy period of time, and therapy is challenging, significantly impacting the patients' quality of life. Currently, there is a deficiency of precise therapeutic modalities and pharmaceuticals in clinical practice[2]. This study provides a summary of the drug and food homologous substances and their role in treating FC. The aim is to offer more effective treatment alternatives for people suffering from this condition.

2 FC

FC is a form of functional gastrointestinal disorder. An introduction of a group of symptoms that introduce difficult bowel movement, reduced frequency of bowel movement and hard bowel movement without obvious organic disease. Its pathogenesis is complex, including eating habits, intestinal flora disorders, neuromuscular regulation disorders and so on. In traditional Chinese medicine, FC is classified under the categories of "Constipation", "Tenesmus", "Difficulty in defecation", and "Spleen constipation"[3]. The escalating prevalence of FC can be attributed to shifts in dietary habits, an accelerated tempo of living, and a complex interplay of social and psychological factors. Global

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epidemiological assessments have estimated the prevalence of FC to be a concerning 14%[4]. Within the Chinese demographic, the incidence varies from 4% to 10%, with a noteworthy trend of increasing prevalence in conjunction with advancing age[5]. In medical practice, the term "functional constipation" is often employed as a synonym for persistent constipation, with diagnosis typically anchored in the Rome III criteria. According to these criteria, FC is delineated by the presence of symptoms over the preceding three months, with an inception dating back at least 6 months. Additionally, there must be at least two other symptoms related to bowel movements. More precisely, the diagnostic criteria for FC in adults must encompass two or more of the subsequent symptoms: Approximately 25% of bowel movements are characterized by the act of forcefully expelling feces, another 25% involve the presence of lumps or hardened stool, a further 25% are incomplete defecations, and another 25% are hindered by blockages in the rectum or anus. Moreover, it is noteworthy that in over a quarter of cases, bowel movements necessitate manual intervention to facilitate the process. The typical frequency of defecation for individuals with FC falls short of the weekly threshold of three occurrences. Additionally, the occurrence of loose stools is a rare phenomenon unless laxatives are consumed to mitigate the condition[6]. The development of FC is intricate and there is a dearth of precise treatment modalities and medications. The primary approach for treating FC in the majority of patients involves self-management measures, including modifying one's lifestyle and utilizing over-the-counter laxatives. Although they have certain short-term efficacy, they are prone to adverse reactions and drug resistance after long-term treatment, leading to poor prognosis of the disease[3]. Clinically, we mainly focus on the following aspects of medication for patients with FC. 1) Increase the frequency of bowel movements: Certain medications and treatments can stimulate intestinal motility and promote bowel movements and defecation, thereby increasing the frequency of bowel movements. This is usually achieved by stimulating neurons, increasing intestinal smooth muscle contraction, and promoting the delivery of stool through the intestine. 2) Improve intestinal moisture: When treating constipation, drugs containing water-soluble fibers are sometimes used. These fibers can absorb water, increase the volume of stool, and make it soft and easy to discharge. Furthermore, several therapies can also modulate the assimilation and excretion of water in the colon, facilitating the passage of feces through the intestinal tract. 3) Promote intestinal peristalsis: Some treatments can directly stimulate intestinal smooth muscle contraction, thereby enhancing intestinal peristalsis and promoting the transmission of stool. 4) Softening the stool: For conditions in which too much water is absorbed in the stool, the stool can be softened by using salt-like drugs, such as salt purgants or osmotic drugs, to return the water in the stool to the intestine. 5) Enhance gut microbiota: Certain medicines address constipation by optimizing the equilibrium of gut bacteria. Augmenting the population of advantageous microorganisms in the gastrointestinal tract can enhance the process of breaking down food and absorbing nutrients, facilitate the movement of the intestines, and decrease the likelihood of experiencing constipation. Figure 1 delineates the plausible pathways through which the medicine food homologous bioactive ingredients may alleviate FC.

3 Concept and classification of MFH substances

Ancient China is the birthplace of the homology theory of medicine and food. The concept of "medicine and food homology" was mentioned in the Huang Di Nei Jing Tai Su: 'To satisfy hunger is called food, to cure disease is called medicine'. The hypothesis of homology of medicine and food has gained increasing application in our country after a prolonged period of development. Many medical-diet books and ancient books have recorded the homology substances of medicine and food which can improve gastrointestinal function, and people have widely used them in medical-diet, diet therapy and diet maintenance[1]. At the same time, with the accumulation of people's health practices, the concept of homologous medicine and food and homologous substances continue to develop and enrich. In 2012, the Ministry of Health released a notice that aims to enhance the regulation of raw ingredients used in health food, encompassing both food and medicine. MFH refers to the concept where certain classes of food possess properties that can be utilized therapeutically. MHF, also known as functional foods, are specific types of foods that are not intended to cure diseases but can regulate human body functions. Up to now, the health administration department of The State Council has issued a total of three batches of both food and Chinese herbal medicine list, a total of 102 substances. Table 1 provides a comprehensive overview of the prevalent MFH substances in China, delineating their principal applications across various domains. These homologous substances of medicine and food possess several features and a moderate flavor, and are highly safe. Many active ingredients of these homologous substances have been analyzed in modern research, and they are often used for nursing and health care[7]. In addition, it is found that it has more advantages in regulating gastrointestinal diseases and treating related diseases[8]. In recent years, the scientific community has increasingly directed its attention towards the diverse bioactive constituents found within MFH substances. These constituents have been systematically categorized into six primary groups, each with its unique set of biological activities and potential health benefits. The classification encompasses a range of compounds, including but not limited to "saponins", "flavonoids", "alkaloids", "terpenoids", "polysaccharides", and a spectrum of other bioactive molecules[9]. In this comprehensive review, the authors have meticulously examined and appraised the advancements in research pertaining to the bioactive ingredients of MFH substances over the recent years. The bioactive ingredients mainly used to treat or improve FC include "polysaccharides", "polyphenols", "saponins", etc.

4 The bioactive substances in the MFH improve FC

4.1 Polysaccharides

Plant polysaccharides are a kind of homologous substances with rich biological activities. The research in the realm of medicine and food homologous plants is currently focused on studying the active polysaccharides derived from these plants. Polysaccharides are intricate natural macromolecules, arising from the condensation of ten or more monosaccharide units or their derivatives, which are linked through glycosidic bonds to form complex chains[10], and is one of the most important active components in medicinal and edible homologous plants. Homologous plant polysaccharides are distributed in the roots, stems, leaves and fruits of plants[11], moreover, these complex molecules exhibit a myriad of biological activities, including antibacterial properties, the potential to alleviate depressive symptoms, modulation of immune responses, and regulation of

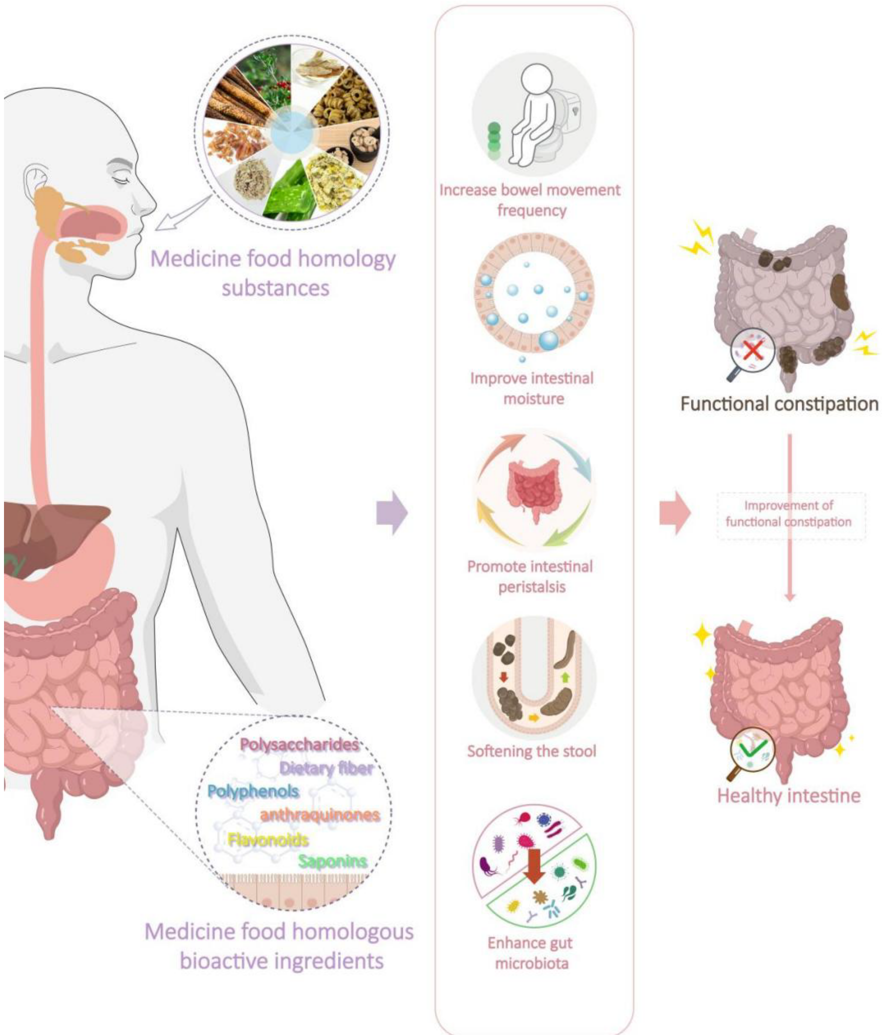


Figure 1 Plausible pathways through which the medicine food homologous bioactive ingredients may alleviate FC.

the intestinal microbiota. Such diverse functionalities position polysaccharides as valuable active constituents in both preventative and therapeutic pharmaceuticals for a spectrum of diseases[12]. For instance, Atractylodis Macrocephalae polysaccharide acts on prebiotics, controlling the population of gut bacteria and facilitating the reestablishment of a healthy balance in the gut microbiota. This dual management of intestinal problems enables it to effectively cure both diarrhea and constipation[13]. Furthermore, Liu *et al.*[14] conducted a study to investigate the impact of Cistanchis polysaccharides on constipated rats suffering from irritable bowel syndrome. The experiment demonstrates that Cistanchis polysaccharides have the capacity to impede the activation of the NGF/TrkA signaling pathway, reduce the generation of 5-hydroxytryptamine, and ameliorate both visceral hypersensitivity and gastrointestinal tract motility in constipated rats. Consequently, these polysaccharides have been demonstrated to mitigate the advancement of constipation in rats afflicted with irritable bowel syndrome. Extensive research indicates that *Dendrobium*-derived polysaccharides possess the capacity to alleviate constipation by enhancing intestinal motility, augmenting the water content of stool, and elevating the concentrations of intestinal hormones, thereby presenting a promising avenue for therapeutic intervention. Moreover, Luo *et al.*[15] conducted an experimental study to investigate the cathartic properties of *Dendrobium officinale* ultrafine powder on constipation in mice and its potential mechanism. The findings indicates that the mean diameter (d50) of the *D. officinale*'s ultrafine powder, obtained through the process of ball milling, measured 6.56μm. Administration of *D. officinale* in its ultrafine powdered form, at dosages ranging from 62.5 mg/kg to 250 mg/kg via the oral route, has been shown to significantly accelerate gastrointestinal transit and promote fecal excretion. The underlying mechanism is hypothesized to involve the upregulation of key gastrointestinal motility factors, including acetylcholinesterase (AChE), gastrin (Gas), motilin (MTL), and substance P (SP), concurrent with a downregulation in the production of somatostatin (SS), thereby modulating the gut's neuroendocrine signaling. Investigations have revealed that the consumption of *D. officinale* in its ultrafine powdered form exerts a significant influence on circulating levels of various gastrointestinal biomarkers, including AChE, Gas, MTL, and SP, suggesting its potential role in modulating digestive function. Additionally, it has been observed to drastically decrease the presence of SS in the bloodstream. The finely ground particles of *D. officinale* possess the potential to be further advanced as an efficacious dietary treatment for constipation. Similarly, in their study, Hao and colleagues[16] developed a rat model of constipation induced by loperamide hydrochloride to investigate the therapeutic potential of Platycodon polysaccharides in alleviating

Table 1 Prevalent categories of MFH in China and their primary utilizations

Origin (Latin name/English name/Pinyin)	Pharmacological action	Applications in the field of food	Applications in the field of medicine	References
Chrysanthemum morifolium Ramat./Chrysanthemi Flos/Juhua	Anti-inflammatory, antiviral, antibacterial, antioxidant	Chrysanthemum cake, chrysanthemum tea, chrysanthemum wine	Compound Chrysanthemum Granules	[53]
Platycodon grandiflorum (Jacq.) A. DC./Platycodonis Radix/Jiegeng	It possesses the properties of an expectorant, antitussive, anti-tumor, and immune system enhancer	Pickling and cooking	Compound Platycodon Cough Tablets, Tangerine Peel Tablets	[54]
Lycium barbarum L./Lycii Fructus/Gouqizi	Antioxidant, anti-neoplastic, liver protection	Soaking water, cooking soup, and making porridge	Qijudihuang Soft Capsule, Zhikang Granules	[55]
Siraitia grosvenorii (Swingle.) C. Jeffrey ex A. M. Lu et Z. Y. Zhang/Siraitiae	Antioxidant activity, hypoglycemic effect, immune effect and hepatoprotective effect	Monk fruit fermented wine, monk fruit cake, monk fruit preserves, monk fruit	Luo Han Guo Xue Li Paste, Luo Han Guo Throat Tablets, Compound Luo Han Guo Cough Granules	[56]
Hippophae rhamnoides L./ Hippophae Fructus/Shaji	Antineoplastic impact, impact on cardiovascular and gastrointestinal systems	Seabuckthorn probiotic jam, seabuckthorn drink or direct consumption	Seabuckthorn Huangtong Soft Capsule, Seabuckthorn Seed Oil Soft Capsule	[57]
Crataegus pinnatifida Bge./Crataegi Fructus/Shanzha	The cardiovascular system is impacted, including effects on cholesterol levels, reduction of edema, and lowering of blood sugar levels	Utilized in confectionery, pastries, beverages, or consumed in its raw form	Shanzha Neixiao Pills, Shanzha Jiangzhi Pills	[58]
Prunus mume (Sieb.) Sieb. et Zucc./ Mume Fructus/Wumei	Antibacterial, antitussive, antiviral, hypoglycemic effects	Preserved fruit or eaten directly	Wumei Pills	[59]
Dioscorea opposita Thunb./ Dioscoreae Rhizoma/Shanyao	Enhance immune system performance, optimize digestive function, reduce blood cholesterol levels, decrease blood sugar levels, and exhibit anti-tumor properties	Make dishes, yam porridge	Stomach-strengthening and Digestion-Promoting Tablets	[60]
Illicium verum Hook. f./Anisi Stellati Fructus/Bajiaohuixiang	Antibacterial, analgesic, antioxidant	For spices and flavors	Fennel Pills, Fennel Oil	[61]
Codonopsis pilosula (Franch.) Nannf/ Codonopsis Radix/Dangshen	Control blood glucose levels, boost immune function, and decrease inflammation	Used in soup, porridge, steamed rice, stir-fry, hot pot ingredients, wine, dried fruits, etc.	Bazhen Pills, Sijunzi Pills	[62]
Cistanche deserticola Y.C. Ma/ Cistanches Herba/Roucongrong	Boost immune system, combat oxidative stress, safeguard liver, provide neuroprotective effects	For dishes, wine and tea	Cistanche Bushen Pills, Compound Cistanche Capsules	[63]
Astragalus membranaceus (Fisch.) Bge. var. mongholicus (Bge.) Hsiao/Astragali Radix/Huangqi	Enhance immune activity and produce therapeutic benefits on the respiratory, digestive, and cardiovascular systems	Utilized in culinary preparations, as well as in the creation of porridge and wine	Astragalus Oral Liquid, Compound Astragalus and Angelica Tablets	[64]
Glycyrrhiza uralensis Fisch./ Glycyrrhizae Radix Et Rhizoma/Gancao	The compound exhibits adrenocortical hormone-like properties, acts as an anti-peptic ulcer agent, possesses immunosuppressive effects, and demonstrates antiviral activity	For tea and spices	Compound Glycyrrhizin Tablets	[65]
Rehmannia glutinosa Libosch./ Rehmanniae Radix/Dihuang	Regulate immune function, enhance hematopoietic function, and protect the cardiovascular system	Stew	Liuwei Dihuang Pills	[66]
Aloe barbadensis Miller/Aloe/Luhui	Anti-neoplastic, hypoglycemic	Aloe vera drinks, aloe vera yogurt	Aloe vera drinks, aloe vera yogurt	[67]
Mentha haplocalyx Briq./Menthae Haplocalycis Herba/Bohe	Effectiveness against tumors, therapeutic effectiveness on the nervous system and digestive system	Prepare dishes, cakes, drinks and sweets	Fangfeng Tongsheng Pills, Ganmao Qingre Granules	[68]
Coix lacryma-jobi L. var. *mayuen.* (Roman.) Stapf/Coicis Semen/Yiyiren	Anti-neoplastic, immunostimulatory, hypoglycemic, hypolipidemic	Job's tears porridge and Job's tears tea	Job's Tears Soup	[69]
Ophiopogon japonicus (L.f) Ker-Gawl./Ophiopogonis Radix/Maidong	Anti-myocardial ischemia, antithrombotic, hypoglycemic	Tea	Shengmai Injection, Shengmai Powder	[70]
Gynostemma pentaphyllum (Thunb.) Makino/Fiveleaf gynostemma herb/Jiaogulan	Neuroprotective, anti-tumor, hypoglycemic, immunological regulating, various other qualities	Tea	Gynostemma Pentaphyllum Saponin Tablets	[71]
Plantago asiatica L./Plantaginis Herba/Cheqiancao	Antibacterial, diuretic and antioxidant effects	Cooking	Milin Capsules, Niushitong Pills	[72]

intestinal dysmotility. The experiment was meticulously designed to assess the capacity of these polysaccharides to normalize gut motility in the context of constipation. They also studied the potential mechanism behind this effect. The study's experimental results underscored the efficacy of Platycodon polysaccharide in significantly ameliorative effects on gastrointestinal motility. Specifically, after a 21-day therapeutic intervention with dosages of 400 and 800 mg/kg, there was a notable enhancement in fecal water content, accelerated stomach emptying, and expedited intestinal transit rate, indicating the potential of Platycodon polysaccharide as a therapeutic agent for dysmotility. Furthermore, there was an elevation in the release of hormones Gas and MTL, which are associated with movement. Results garnered from a suite of biochemical assays, including the enzyme-linked immunosorbent test, protein blotting, immunohistochemistry, and immunofluorescence, have collectively illustrated a marked elevation in the secretion of 5-HT and the synthesis of its associated proteins upon treatment with Platycodon polysaccharide. Furthermore, an in-depth analysis empowered by 16S rRNA gene sequencing has revealed that Platycodon polysaccharide exerts a profound impact on the prevalence of specific bacterial genera, namely *Roseburia*, *Butyricimonas*, and *Ruminiclostridium*, within the gut microbiota. Strikingly, a robust positive correlation was identified between Platycodon polysaccharide concentrations and 5-HT levels, underscoring the polysaccharide's potential role in modulating the gut's neuroendocrine landscape. Platycodon polysaccharide enhances the movement of the intestines by controlling the concentration of 5-HT. The neurotransmitter 5-HT plays a pivotal role in modulating the intricate interplay between the gut microbiota and the intestinal neuroendocrine system, thereby significantly influencing the pathophysiology of constipation. Building on this foundation, emerging research underscores the beneficial effects of chrysanthemum polysaccharides in ameliorating FC, offering a promising avenue for therapeutic intervention[17], the mechanism by which chrysanthemum polysaccharides improve constipation has been investigated using proteomics and the study of intestinal flora. Chrysanthemum polysaccharides have demonstrated remarkable efficacy in enhancing the hydration of fecal matter, thereby facilitating intestinal content movement. Additionally, these polysaccharides stimulate the endogenous production of key gastrointestinal motility regulators, including MTL, Gas, and SP, in a rat model. Concurrently, they exert an inhibitory effect on SS levels, which is often associated with the inhibition of gastrointestinal propulsion, and improving gastrointestinal motility. Studies on the intestinal microbiome have demonstrated that chrysanthemum polysaccharides have a substantial impact on increasing the abundance of different species and enhancing the diversity and organization of the microbial community. Proteomics research has demonstrated that chrysanthemum polysaccharides can decrease damage to the intestines, by modulating the expression of Rat Sarcoma Proteins, Fatty Acid Binding Protein 1, and Solute Carrier Family 1 Member 5, these interventions effectively enhance intestinal homeostasis, expedite the absorption of amino acids, invigorate intestinal motility, and mitigate the symptoms of constipation. This approach underscores the potential of targeted protein expression in recalibrating gastrointestinal function and providing relief from constipation. The study findings demonstrate that chrysanthemum polysaccharides have the capability to regulate FC, hence offering a possible therapeutic target for treating disorders in individuals with FC.

4.2 Polyphenols

4.2.1 Probiotic-promoting polyphenols

Polyphenols are secondary metabolites characterized by their polyphenolic structure, they have a broad distribution throughout the fruits, roots, skins, leaves, and other tissues and organs of plants, their content ranks just behind that of cellulose, hemicellulose, and lignin[18]. Due to their natural origin and few side effects, these substances are considered a valuable repository of green, eco-friendly, and renewable resources. Plant polyphenols possess an intricate composition and can be classified using several ways. Scholars acknowledge the categorization of polyphenols based on their plant origins. Currently, over 8,000 natural phenolic compounds and their derivatives have been discovered and characterized in the natural world[19]. Plant polyphenols possess a diverse range of physiological roles, and the majority of plants contain varying quantities and types of these compounds. Plant polyphenols derived from various sources have distinct biological activities. Through structural alteration, these polyphenols frequently demonstrate enhanced biological activity and improved therapeutic effectiveness[20]. Emerging research compellingly illustrates the pivotal role of polyphenols in safeguarding against a spectrum of degenerative diseases. Their preventive capacity is particularly evident in the realms of cancer, cardiovascular disease, and neurological disorders, underscoring their significance in public health and disease management[21]. The direct and clear therapeutic effect of plant polyphenols on constipation is uncertain. Currently, there is no scientific data suggesting that plant polyphenols have a direct therapeutic impact on constipation. Plant polyphenols have the ability to indirectly improve intestinal health by regulating the makeup of the intestinal microbiota, which may help alleviate symptoms of constipation. The dynamic interplay between the gut microbiota and phenolic compounds exemplifies a symbiotic relationship of significant biological consequence. The gut microbiota plays a crucial role in modulating the bioaccessibility of phenolic compounds, which in turn has profound implications for human health. Specifically, phenolic compounds that escape absorption in the small intestine contribute to the nourishment of the intestinal microbiota, thereby altering the metabolic potential and nutritional profile of these dietary phytochemicals[22]. The scientific community is witnessing a surge in research dedicated to unraveling the intricate relationship between the gastrointestinal microbiota and intestinal function. This burgeoning field of study is particularly focused on the role of probiotics in modulating intestinal motility and their potential to alleviate constipation, highlighting the significance of a balanced gut ecosystem in digestive health[23]. The findings from a recent systematic review and meta-analysis have shed light on the potent effects of specific probiotic species and strains when consumed at dosages between 10^8 and 3×10^{10} CFU/day. This consumption pattern has been associated with a notable reduction in intestinal transit time by up to 12 h, a significant increase in bowel movement frequency by 1.5 times weekly, and the mitigation of various symptoms related to constipation[24]. In addition, research has demonstrated that some polyphenol compounds can function on gut probiotics, similar to *Bifidobacterium* and *Lactobacillus*, resulting in positive effects on human health. In a pioneering study conducted by Tzounis *et al.*[25] in 2008, the researchers delved into the bidirectional metabolic dynamics between human gut microbiota and the flavan-3-ols, (−)-epicatechin and (+)-catechin. They employed a sophisticated pH-controlled, stirred batch culture fermentation model, designed to emulate the conditions of the large intestine's distal region, thereby providing critical insights into the metabolic interplay of these phenolic compounds with our gut bacteria. Tzounis *et al.*'s research[25] uncovered that (+)-catechin exerts a notable influence on the proliferation of specific bacterial groups within the gut microbiota. Specifically, this compound was found to induce a substantial increase in the population of the *Clostridium cocci*-Eubacterium rectum cluster and *Bifidobacterium* species, highlighting its potential prebiotic effects. Continuing the exploration of the impact of catechin isomers on gut microbiota, the study observed a stark contrast in their influence. While (+)-catechin significantly inhibited the proliferation of the *Clostridium histolyticum* group, (−)-epicatechin showed a muted effect, yet notably stimulated the growth within the *C. histolyticum*-Eubacterium rectum group. The prebiotic efficacy of both compounds peaked at a concentration of 150 mg/L, suggesting an optimal threshold for their beneficial activity. Intriguingly, the variations in microbial growth patterns in response to (+)-catechin could be attributed to its microbial transformation into (−)-epicatechin, as both compounds culminate in the production of identical metabolites, illustrating the intricate biotransformation processes at play within the gut ecosystem. Furthermore, anthocyanidins, the quintessential pigments responsible for the vibrant red, blue, and purple hues observed in the petals of flowers, the flesh of fruits, the richness of vegetables, and even in select grains like black rice, play a central role in the colorful tapestry of the natural world. Predominantly existing in plants as glycosides, these compounds are widely recognized under the collective term "anthocyanidins", contributing not only to the visual appeal but also to the health-promoting properties of numerous plant-based foods[26]. In a pioneering study by Hidalgo *et al.*[27] in 2012, an artificial model of the human intestinal environment was employed to scrutinize the microbial metabolism of a complex mixture comprising malvidin-3-glucoside, gallic acid, and anthocyanidins. The findings illuminated the capacity of anthocyanidins to markedly stimulate the proliferation of beneficial gut bacteria, specifically *Bifidobacterium* and *Lactobacillus*-Enterococcus species. This discovery underscores the potential of anthocyanidins and their metabolites to exert selective enhancement of advantageous microbial populations within the gut microbiota, thereby contributing to a balanced and healthy gut ecosystem[27]. Additionally, in a groundbreaking 2009 investigation by Bialonska and colleagues[28], the impact of pomegranate peel extract, particularly its predominant polyphenol punicalagin, was meticulously examined concerning its influence on the proliferation of various human intestinal bacteria. The study aimed to unravel the nuances of how these botanical compounds interact with and potentially benefit our gut microbiota. The researchers used an *in vitro* experiment in a liquid culture to carry out their investigation. Punicalagin is a complex polymer consisting of ellagic acid and a polyphenolic component found in the peel of pomegranates. Due to the presence of glycosides, it exhibits high water solubility and is readily absorbed by the human body. Once it enters the human body through the stomach and intestines, it undergoes degradation to produce ellagic acid. The experiment demonstrated that the utilization of pomegranate peel extract resulted in an augmentation of the overall bacterial count and facilitated the proliferation of bifidobacteria, lactobacilli, and enterococci[28]. While there is currently no conclusive data supporting the use of plant polyphenols for treating constipation, it is evident that these compounds have an indirect effect on gut microorganisms, which can help alleviate constipation symptoms in patients. Further scientific inquiry is warranted to fully elucidate the therapeutic potential of plant polyphenols as novel agents in the management of constipation. This research will be instrumental in assessing their efficacy, safety, and mechanisms of action within the complex milieu of the gut. Figure 2 presents the structure of some probiotic-promoting polyphenols compounds that act on constipation.

4.2.2 *Anthraquinones*

Anthraquinone compounds, exemplified by the dianthrone derivatives sennoside A and sennoside B, function as potent natural stimulant laxatives. They exert profound influences on the gastrointestinal tract, notably enhancing its motility and providing substantial relief for individuals suffering from FC[29]. Anthraquinones are a type of chemical compounds that are present in certain plants. They are typically categorized as phenolic compounds and are known for their clear and noticeable ability to alleviate constipation. Anthraquinone molecules can be found in several chemical forms, including free anthraquinone, anthraquinone glycosides, anthrone, and dianthrone[30]. For instance, aloe vera is a well-known and commonly used health supplement that offers several advantages. Additionally, it possesses a distinct ability to alleviate constipation[31]. Aloe vera's notable laxative properties can be attributed to the presence of specific anthraquinone glycosides, with aloesin A and B being key contributors to its efficacy in promoting bowel movements. Aloe vera includes not only aloesin (10%–30%), but also a significant quantity of volatile compounds (16%–63%) and volatile oils. Aloe vera exhibits a potent laxative action among the anthraquinone chemicals. Administering a dosage of 0.25 g will result in a laxative impact within a time frame of 6–12 h, causing loose stools and abdominal discomfort[32]. Furthermore, rhubarb is rich in sennoside A, a compound that acts as a laxative, and it also contains significant quantities of tannins. The chemical sennoside A is principally responsible for the observed laxative effect of this stimulant laxative. Nevertheless, the improper utilization of it frequently results in abdominal pain or intestinal cramps, whereas research has indicated that doses ranging from 0.5 g to 2 g do not induce abdominal pain[30]. Prolonged utilization of rhubarb

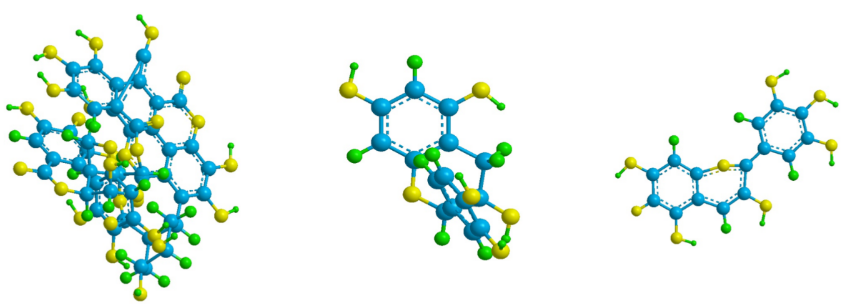


Figure 2 Structure of probiotic-promoting polyphenols compounds that act on constipation.

containing sennoside A can result in the development of drug resistance or potentially harmful responses, hence restricting its application in clinical settings. In a pivotal study conducted by Zhang and colleagues[33], it was determined that the consistent application of sennoside A for a duration of less than a week effectively alleviates constipation. Notably, this treatment regimen demonstrated no discernible adverse effects on colonic health over the subsequent 7-day observation period. Moreover, the laxative mechanism of sennoside A was elucidated to involve modulation of the intestinal microbiota, enhancing the presence of beneficial bacteria such as *Lactobacillus*, *Akkermansia*, and the UCG_005 group. The study also highlighted the role of aquaporin channels, specifically Aquaporin 1 and Aquaporin 3, in facilitating the hydrating effects necessary for sennoside A's laxative action[33]. Particularly, senna is unquestionably the most widely utilized among all the anthraquinone laxatives. Senna's potent laxative properties are primarily attributed to the presence of its physiologically active constituents, with sennosides A and B being the principal contributors. In addition to these, the presence of other anthraquinone derivatives, including aloe-emodin and rhein, further augments the overall laxative efficacy of senna. Senna is more commonly employed due to its comparatively gentle impact and lower cost. Certain individuals suffering from constipation opt to steep senna leaves in chilled water for a duration of 10–12 h, thereafter preparing it as a beverage following the process of filtration. This preparation is more potent than hot tea due to its higher concentration of sennosides and lower presence of resinous compounds[30]. Figure 3 presents the structure of some anthraquinone compounds for treating constipation.

4.2.3 Flavonoids

Flavonoids possess phenolic characteristics and belong to the category of polyphenols[30]. Flavonoids represent a significant group of naturally occurring chemical compounds, distinguished by their defining 2-phenyl-chromone structure. These bioactive molecules are ubiquitously found throughout the plant kingdom, contributing to the rich diversity of botanical life[34]. Flavonoids exhibit an extensive array of pharmacological properties, endowing them with the capacity to act as anti-inflammatory agents, combat bacterial infections, support cardiovascular health, and provide neuroprotection. The diverse health benefits offered by these compounds have garnered considerable attention from the pharmaceutical industry, particularly those flavonoids with robust antioxidant capabilities and the ability to neutralize free radicals, positioning them as promising candidates for therapeutic development[35]. Recent research has discovered that flavonoids has medicinal and preventative properties that can alleviate constipation. Such as, Chen *et al.*[36] provided a partial explanation for the effectiveness of Xiebai in treating constipation. They identified two factors that contribute to its efficacy: maintaining the amount of water in the colon and boosting the movement of the intestines. In the loperamide-induced mouse model of constipation, the oral administration of a 50% ethanol extract of Xiebai for 9 days led to an augmentation in the water content of the intestinal wall. It also regulated the rhythm of intestinal motility and restored regular defecation. This activity is linked to a reduction in the production of colonic AQP3 and an increase in the activation of G protein α (Gα) and phosphoinositide 3-kinase (PI3K). Furthermore, they conducted tests to assess the impact of chemicals derived from Xiebai on intestinal motility. The findings demonstrated that the three primary flavonoids had a notable impact on elevating the calcium ion levels in HCT116 cells and stimulating the contraction of mouse intestinal smooth muscle. These activities may be associated with M cholinergic receptors, μ opioid receptors, 5-HT3 receptors, and 1, 4, 5-trisphosphate inositol (IP3) receptors. Furthermore, luteolin, a naturally-occurring flavonoid, has been found to possess potential pharmacological properties in combating intestinal inflammation and neural damage. Wang and colleagues[37] meticulously designed an experimental study to elucidate the therapeutic role and intricate mechanisms of luteolin on FC in mice induced by loperamide. The experimental outcomes demonstrated that the administration of luteolin effectively normalized the frequency of bowel movements, increased the moisture content of the stools, and decelerated the intestinal transit time in the loperamide-induced constipation mouse model. These findings indicate luteolin's potential in mitigating the symptoms of FC. Moreover, the study observed that luteolin extended the intestinal transit time for substances, potentially indicating its influence on the motility of the gastrointestinal tract. Additionally, luteolin was found to augment the muscularis mucosae thickness, thereby mitigating the histological injuries to the colon induced by loperamide, which is a significant advancement in the therapeutic approach to constipation. Building upon their findings, Wang *et al.*[37] revealed that luteolin administration is associated with the upregulation of neuronal protein HuC/D, alongside an increase in critical biomarkers of intestinal motility, including SP, vasoactive intestinal polypeptide (VIP), and ACh. These insights underscore the compound's potential in modulating gut motility. Moreover, luteolin was observed to enhance biomarkers pertinent to interstitial cells of Cajal (ICC), such as the KIT proto-oncogene, the receptor tyrosine kinase C-Kit, and anti-octylamine-1 (ANO1), which are instrumental in the gut's pacemaking activity. The collective results suggest that luteolin not only bolsters colonic function but also ameliorates motility irregularities in the context

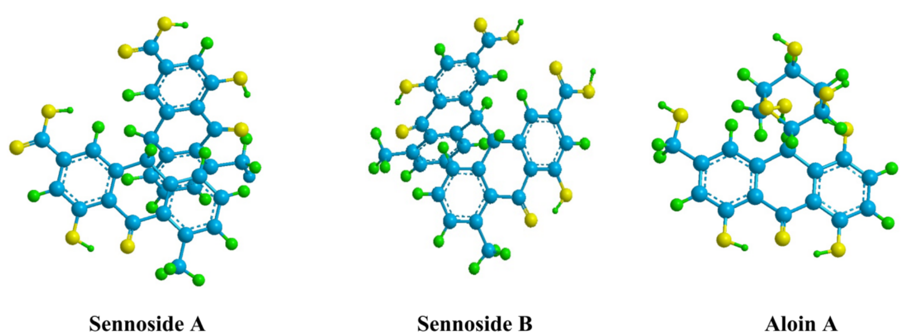


Figure 3 Structure of anthraquinone compounds for treating constipation.

of loperamide-induced FC in mice. In an additional layer of impact, luteolin demonstrated the capacity to attenuate the overexpression of aquaporin water channel proteins AQP3, AQP4, and AQP8 in the colonic mucosa of affected animals, thereby addressing a key pathological feature of constipation. The research conducted by Wang *et al.*[37] indicates that luteolin shows potential as a viable option for developing drugs to relieve FC. In addition, Hu *et al.*[38] have shown that the main active compound (ATTF) present in *Amomum tsaoko* (AT) extract can relieve constipation via influencing the composition of intestinal microbes and the synaptic pathways of 5-HT. AT is a botanical plant that has a purgative impact when consumed as part of a diet. Nevertheless, the specific components responsible for its effects and the exact mechanisms by which it acts as a laxative are still not fully understood. The ethanol-soluble fraction (ATES) of *A. tsaoko* water extract (ATAE) is the active substance that stimulates bowel movements in mice suffering from chronic transmission constipation. The primary active components in ATES are the total flavonoids (ATTF). Administration of the ATTF has been shown to markedly enhance the gut's beneficial bacterial populations, such as Lactobacillus and Bacillus, while simultaneously curbing the dominance of certain commensal bacteria, including those categorized as Laxative bacteria. This intervention effectively reshapes the gut microbiota's structure and composition. Concurrently, ATTF modulates the intestinal metabolome, particularly focusing on pathways pivotal to serotonergic signaling. Furthermore, ATTF is observed to elevate blood serotonin (5-HT) levels and to stimulate the synthesis of key molecules involved in serotonergic synaptic transmission, including the 5-hydroxytryptamine receptor 2A (5-HT2A), phospholipase A2 (PLA2), and cyclooxygenase 2 (COX2). The augmentation of transient receptor potential A1 (TRPA1) by ATTF initiates a cascade that enhances 5-HT secretion and activates myosin light chain 3 (MLC3), thereby facilitating smooth muscle contraction and contributing to the alleviation of constipation. The aforementioned findings indicate that ATTF may alleviate constipation by modulating the composition of intestinal microorganisms and the signaling pathways involving 5-HT, hence demonstrating significant promise in the advancement of novel laxative medications. In addition, quercetin, a distinguished member of the flavonoid subclass, is renowned for its bioactivity and a molecular framework characterized by the flavonoid skeleton of nC6 (ring A) linked to C3 (ring C) and C6 (ring B)[39]. Liu *et al.*[40] spearheaded an inquiry into the protective prowess of quercetin against loperamide-induced constipation in rats, probing its intrinsic mechanisms. The findings illuminated that the oral administration of quercetin at concentrations of 25 and 50 mg/kg to the rats led to a pronounced enhancement in small intestinal motility. Furthermore, it stimulated an upregulation in the production of gastrointestinal motility regulators such as MTL, Gas, SP, and short-chain fatty acids, thereby reinforcing the intestinal propulsion. Furthermore, it resulted in a decrease in SS levels and an enhancement in gastrointestinal motility. A study demonstrates that quercetin has a beneficial impact on constipation induced by loperamide. This effect is likely due to quercetin's ability to regulate several signaling pathways[40]. Figure 4 presents the structure of some flavonoid compounds for treating constipation.

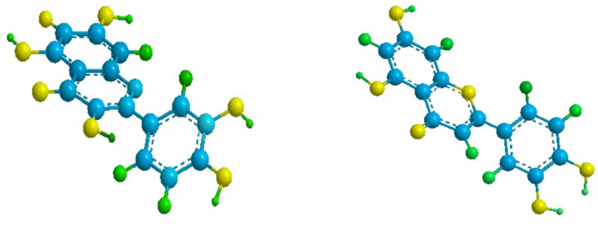


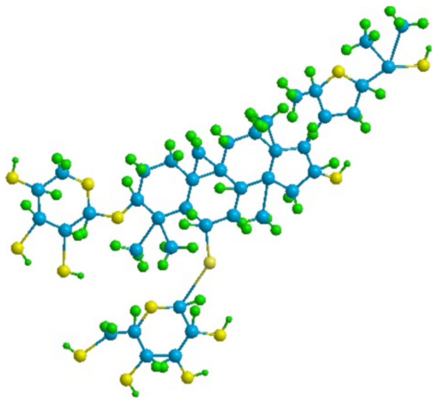
Figure 4 Structure of flavonoid compounds for treating constipation.

4.3 Saponins

Saponins, a class of glycoside compounds, are ubiquitous within the botanical realm. These molecules are intricately structured around a steroidal or triterpenoid aglycone core, to which one or several sugar chains are attached[41]. The diverse array of biological and pharmacological activities exhibited by saponins is well-documented in scientific literature[42]. Recently, there has been a resurgence of interest in saponins derived from both nutritional and non-nutritional sources, propelled by the accumulating scientific evidence that underscores their salutary effects. These include the capacity to reduce cholesterol levels and exhibit anti-neoplastic properties[43]. Empirical studies have established that saponin compounds possess distinct medicinal attributes capable of mitigating constipation. A case in point is astragaloside IV (AS-IV), a saponin derivative characterized by its limited drug permeability, which has been shown to exert beneficial effects on individuals afflicted with chronic transit constipation. However, the underlying mechanisms by which AS-IV modulates this condition remain to be elucidated. In a recent experimental investigation led by Wan and colleagues[44], the therapeutic impact of AS-IV on loperamide-induced chronic transit constipation in mice was assessed. The study's parameters included the frequency of bowel movements, intestinal motility, enterochromaffin cell count, and colonic integrity in mice afflicted with chronic constipation that received AS-IV treatment. The findings demonstrated that administration of AS-IV enhanced bowel movements, enhanced the functioning of the intestines, suppressed the depletion of enterochromaffin cells, and mitigated colon damage in mice suffering from chronic transit constipation. Besides, Kim and colleagues[45] recently explored the efficacy of saponin-enriched *Asparagus cochinchinensis* extract (SPA) in mitigating constipation and its associated inflammatory and muscarinic cholinergic responses in a rat model. This study revealed that the group administered loperamide alongside SPA exhibited significant enhancements in fecal output, gastrointestinal motility, mucosal thickness, surface morphology, Paneth cell density, and lipid content, contrasting markedly with the group treated with loperamide and a control vehicle. Treatment with Saponin-enriched SPA resulted in the normalization of key pro-inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6, alongside the downregulation of inflammatory mediators nuclear factor-kappa B and inducible nitric oxide synthase. Furthermore, SPA therapy effectively reduced mast cell infiltration in the affected areas and promoted mucin synthesis. The findings underscore the extract's potential to initiate anti-inflammatory processes and modulate muscarinic cholinergic activity, thereby exerting a laxative influence in a loperamide-induced chronic constipation model[45]. Figure 5 presents the structure of some saponin compounds for treating constipation.

4.4 Other MFH substances effect on FC

The medicinal significance of honey is chronicled in some of



Astragaloside

Figure 5 Structure of saponin compounds for treating constipation.

the earliest medical texts, revered throughout history for its potent antimicrobial characteristics and its remarkable ability to expedite the wound healing process[46]. Honey, a natural nutrient with distinctive composition and inherent antimicrobial attributes, is recognized for its role in fostering the growth of beneficial bifidobacteria. In a study by Li and colleagues[47], honey's potential to alleviate loperamide-induced constipation in BALB/c mice was investigated, focusing on its impact on gut microbiota composition. The findings indicated that honey significantly elevated fecal moisture content, thereby mitigating constipation through modulation of the microbiota's microbial balance. This underscores honey's potential as a beneficial indicator in the assessment of therapeutic approaches for constipation[47]. Moreover, seabuckthorn is a highly nutritious and therapeutic food that is considered a health food. Pharmacological studies have shown that specific chemicals present in seabuckthorn have a range of advantages, such as reducing inflammation, preventing oxidative damage, protecting the liver, combating cardiovascular diseases, fighting against cancer, lowering blood sugar levels, reducing lipid levels, safeguarding the nervous system, and killing bacteria[48]. The researchers, Muhammad Hanif *et al.*[49], conducted an experimental study to illustrate the prokinetic and intestine stimulating effects of extracts from seabuckthorn fruit. This study is the first of its kind to uncover the mechanism by which seabuckthorn fruit can act as a laxative. This finding provides a logical explanation for why seabuckthorn fruit is used medicinally to treat constipation. Hawthorn is a type of traditional Chinese medicine that can be consumed and has proven efficacy in treating dyspepsia. In their research, Pei and colleagues[50] harnessed the power of network pharmacology and molecular docking to elucidate the therapeutic targets and mechanisms underlying hawthorn's efficacy in dyspepsia treatment. By integrating these analytical techniques, they dissected the molecular underpinnings of hawthorn's action. The study's findings point towards a multifaceted approach to alleviating dyspepsia, which includes curtailing intestinal inflammation, enhancing gut motility, modulating cellular functions, and easing constipation. This study offers guidelines and a foundation for the future implementation of ingestible medications. In addition, Wei *et al.*[51] conducted trials that validated the efficacy of hawthorn probiotic supplements in alleviating constipation. Recent findings have unveiled the capacity of these dietary supplements to regulate intestinal water and sodium homeostasis, thereby maintaining the intestinal mucosal integrity and fostering a balanced gut microbiota. Mulberries have historically been used to treat gastrointestinal ailments. However, the precise mechanism behind their therapeutic activities remains unclear. As well as this, in a recent inquiry led by Hu *et al.*[52], the therapeutic potential of mulberry supplementation via gavage was scrutinized for its impact on phenoxylate-induced constipation in mice. The study delved into the mechanisms behind mulberry's efficacy by evaluating fecal characteristics, physicochemical properties, histological assessments, and 16S rDNA sequencing of the gut microbiome. The findings illustrated that mulberry intake significantly mitigated constipation, evidenced by enhanced fecal hydration, expedited initial passage of stool, augmented gastric motility, and accelerated transit through the gastrointestinal tract. The study compellingly demonstrates that mulberry intake markedly ameliorates constipation in murine models. Consequently, mulberries present themselves as a promising candidate for an alternative constipation remedy[52]. While the beneficial impact of the aforementioned classes of medicinal and edible homologous substances on constipation has been observed, the definitive bioactive ingredients have not been clearly identified. It is imperative for future research to broaden its scope, engaging in a multitude of experimental inquiries to dissect the bioactive components present within a variety of these substances.

5 Conclusion and future prospects

FC represents a type of functional bowel disorder, predominantly characterized by difficulties in defecation, infrequent bowel movements, or a feeling of incomplete evacuation. The annual incidence of this condition is on the rise due to shifts in dietary habits, an accelerated pace of life, and various social influences. Upon initial diagnosis, patients suffering from FC often opt to use laxatives as a treatment approach. However, despite lifestyle modifications, dietary adjustments, and the use of both over-the-counter and prescription medications, some individuals continue to experience persistent symptoms. In certain cases, patients may even experience severe reactions and develop reduced tolerance to laxatives. MFH substances, a group of natural compounds rich in nutrients and pharmacological effects, have shown potential in the treatment and prevention of FC. Notable bioactive molecules within this category include polysaccharides, polyphenols, and saponins. Plant polysaccharides primarily alleviate constipation by promoting intestinal motility, increasing stool water content, and elevating intestinal hormone levels. Dietary fiber, a type of carbohydrate, primarily enhances intestinal motility by fostering the growth of beneficial bacteria and reducing oxidative stress. It also augments water content in the intestines, softening the stool and aiding in the treatment and prevention of FC. Polyphenol compounds mostly ameliorate constipation symptoms indirectly by modulating the probiotics within the human gut.

Flavonoids, a class of polyphenols present in plants, significantly influence colon water content, promote efficient intestinal transit, and support the proliferation of beneficial bacteria in the digestive system. These effects bear substantial implications for both intestinal and overall human health. Saponin compounds mainly facilitate bowel movements by enhancing intestinal contractions, while AS-IV prevents the depletion of enterochromaffin cells and reduces colonic damage. Polysaccharides found in *Atractylodes macrocephala*, as an example of MFH substances, function as prebiotics, helping regulate intestinal bacteria and restore the balance of the gut flora, thereby effectively treating constipation. Cistanche polysaccharides have the capacity to impede the NGF/TrkA signaling pathway, decrease 5-HT production, and alleviate constipation symptoms. Dendrobium polysaccharides can enhance intestinal motility, increase fecal water content, and raise hormone levels in the intestines. Platycodon polysaccharides effectively reduce gastrointestinal motility, stool water content, gastric emptying rates, and intestinal transit speeds. Chrysanthemum polysaccharides significantly impact the diversity and structure of the gut flora, promoting gastrointestinal movement and alleviating constipation symptoms. Xiebai's primary mechanism for effectively treating constipation involves flavonoids that stimulate the contraction of intestinal smooth muscles. AT extract contains flavonoids that can enhance bowel movements by altering the composition and structure of the gut microbiota. AS-IV enhances intestinal motility and increases the frequency of fecal matter. SPA, rich in saponins, induces anti-inflammatory responses and regulates muscarinic cholinergic activity, contributing to its laxative effects. Catechins notably increase the prevalence of beneficial bacteria, such as the *C. cocci*-rectal eubacterium group, bifidobacterium, and *Escherichia coli*, while suppressing the growth of harmful bacteria. Anthocyanins significantly stimulate the proliferation of bifidobacteria and *Lactobacillus-Enterococcus*. Pomegranate extract's polyphenols stimulate the growth of bifidobacteria, lactobacilli, and enterococci, augmenting the overall probiotic population. Honey effectively increases fecal water content and alleviates constipation by modulating the microbiota's composition. Seabuckthorn fruit extract stimulates intestinal movement, enhancing its motility and effectively relieving constipation symptoms.

The active substances found in MFH offer novel insights for the advancement of new medications targeting FC. Future studies should build on these achievements and further investigate novel bioactive compounds within the field of MFH. Understanding the chemical composition is crucial for grasping the mechanisms of action and optimizing the application of these substances, as their structure directly influences functionality. Network pharmacology and molecular docking methods can predict the potential targets and receptor-binding capacity of small medicinal molecules before live animal experiments. These advanced simulation techniques provide a more precise determination of the active components and their mechanisms of action. Conduct initial assessments of efficacy and organize or participate in multicenter clinical trials to validate the effectiveness and safety of novel medications and confirm their clinical applicability. Explore novel techniques for the extraction and processing of active compounds to enhance the production efficiency of new medications and ensure their stability and efficacy. Foster interdisciplinary collaboration across relevant fields, share resources, and make collective progress in researching the active constituents of MFH.

The active components of MFH have shown great potential in managing FC. Despite the progress in experiments, challenges such as effective separation of active ingredients, ensuring the durability and consistency of effects, and guaranteeing safety remain. Further extensive research and thorough experimentation are needed to address these issues. Additionally, further research is required to reveal the mechanisms by which MFH substances act on FC and to propose more scientifically sound treatment methods. In-depth investigation of safety and dosage issues surrounding MFH substances are necessary, with special attention to the treatment of specific populations, including pregnant women, the elderly, and individuals with pre-existing medical conditions. Our goal is to leverage the advantages of MFH substances to provide additional therapeutic and preventive options for functional intestinal disorders.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work. Min-Hui Li is an associate editor of the journal, but was not involved in the processing, peer review or decision making of this article.

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