Heliyon 10 (2024) e35696

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Acupuncture and moxibustion intervention in functional dyspepsia: Gastric and duodenal regulation

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ARTICLE INFO

Keywords:
Functional dyspepsia
Acupuncture and moxibustion
Gastrointestinal dysfunction
Low-grade inflammation of the duodenum
Visceral hypersensitivity
Duodenal intestinal barrier
Microbiota

ABSTRACT

Functional dyspepsia (FD) is a brain–gut interaction disorder located in the stomach and duodenum, which has complex pathophysiological mechanisms, and there is no effective treatment for FD. Acupuncture and moxibustion have been proven to have definite and significant efficacy on FD. Focusing on the affected area and combined with the potential pathophysiology of FD, here we discuss the possible mechanisms of acupuncture and moxibustion in treating FD to guide future clinical and experimental research. We argue that the pathological causes of FD can be roughly divided into gastrointestinal dysfunction, duodenal low-grade inflammation, visceral hypersensitivity, and duodenal intestinal barrier and microbial imbalance. Correspondingly, the possible mechanisms of acupuncture and moxibustion in treating FD are elucidated from the perspective of how they improve gastric accommodation, regulate gastrointestinal motility, reduce gastric visceral sensitivity, regulate eosinophil–mast cell axis, inhibit low-grade inflammatory responses, and possibly regulate intestinal microbial homeostasis and duodenal barrier function through the microbiota–gut–brain axis. Although some evidence is still lacking, acupuncture remains a promising treatment for FD. In the future, it is necessary to conduct additional clinical and experimental research on acupuncture and moxibustion in treating FD to further explore their effects and mechanisms.

1. Background

Functional dyspepsia (FD) is defined as a disorder of brain–gut interaction [1] characterized by gastrointestinal symptoms in the stomach and duodenum with no incidence of organic lesions. The updated version of the Rome IV criteria describes FD as a

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https://doi.org/10.1016/j.heliyon.2024.e35696
Received 3 May 2023; Received in revised form 31 July 2024; Accepted 1 August 2024
Available online 6 August 2024

postprandial distress syndrome (PDS) with symptoms of postprandial fullness and early satiation and as an epigastric pain syndrome (EPS) with symptoms of epigastric pain and burning [2]. However, there is clinical overlap between PDS and EPS symptoms [3]. PDS has a higher incidence rate than EPS based on an endoscopic examination study of FD [4]. Epidemiological surveys have shown that the incidence of FD is affected by geographical distribution and varies worldwide. The results of the recent Rome Fund global survey on the epidemiology of functional gastrointestinal disorders involving 33 countries on six continents showed that the prevalence of FD in different countries ranged from 2.4 % (Japan) to 12.3 % (Egypt) [5]. The quality of life among patients with FD patients is adversely affected [6], and the disease poses heavy economic burdens [7].

The pathophysiological mechanisms of FD are complex and are not yet fully understood. The current knowledge holds that FD is closely related to gastrointestinal motility disorder, low-grade duodenal inflammation and visceral hypersensitivity (VH), duodenal barrier damage, microbiota disorder, psychological factors, and genetic susceptibility [8](Fig. 1). Conventional treatments for FD include antacids, prokinetic agents, antidepressants, and anxiolytics, but long-term use of these drugs may have certain side effects or induce dependence in the body. Therefore, as an alternative therapy, acupuncture is highly attractive to patients and doctors. As the most widely used traditional medical therapy in the world, acupuncture is commonly applied in gastrointestinal diseases [9,10]. Numerous studies [11–13] have shown that acupuncture and moxibustion can significantly relieve dyspeptic symptoms, alleviate negative emotions such as depression and anxiety, and improve the quality of life of FD patients, with definite long-term efficacy and few adverse reactions. However, the mechanism of acupuncture in treating FD is not clear. Here, we searched PubMed, Web of Science, Embase and Google Scholar with "acupuncture and moxibustion," "acupuncture," "moxibustion," "electroacupuncture," "transcutaneous electrical acupoint stimulation," "functional dyspepsia," and "functional gastrointestinal disorders" as keywords for clinical and animal experimental articles on acupuncture in the treatment of FD. We aimed to explore the potential mechanisms of acupuncture and moxibustion in treating FD from a pathophysiological basis.

2. Acupuncture for the treatment of gastrointestinal function

2.1. Gastric accommodation

Gastric accommodation is a physiological function that allows the proximal stomach to receive large amounts of food through reflex after eating. Studies have reported that approximately 40 % of FD patients have decreased gastric accommodation after meals. Impaired gastric fundic accommodation is closely related to dyspeptic symptoms [14]. For gastric accommodation, a slow nutrient drinking test has been used as a minimally invasive and convenient method to assess PDS symptoms in Japanese FD patients, with good safety and efficacy [15]. The possible mechanism of gastric accommodation is associated with vagal cholinergic signaling to regulate intragastric pressure and intrinsic nerve release of nitric oxide (NO). When a person eats, the vagus nerve is activated and NO is released, which causes the receptive relaxation of the stomach and avoids the excessive rise in intragastric pressure. NO is a major factor in regulating gastric accommodation, and studies have shown that inhibition of NO synthase in healthy volunteers reduces gastric accommodation function and produces symptoms of early satiety [16]. On the contrary, FD patients with impaired gastric accommodation have aggravation of a series of symptoms related to eating, such as early fullness and upper abdominal distension [17]. However, NO inhibitors do not completely inhibit gastric accommodation, and 5-hydroxytryptamine (5-HT) 1A agonists also involved [18]. 5-HT3 and 5-HT4 receptor agonists have also been shown to promote gastric dilatation and relaxation [19]. One study reported that electroacupuncture (EA) improved gastric accommodation in dogs that underwent vagotomy, suggesting that gastric receptivity impairment may be related to mechanisms other than vagal function [20]. The effects of EA may be related to cholinergic nerves, motilin, and cholecystokinin (CCK) [21]. In addition, the improvement of gastric accommodation in diabetic rats by EA stimulation at ST36 could be blocked by naloxone [22], suggesting a possible link with the opioid receptors.

Therefore, the regulation via acupuncture of gastric receptivity is multi-channel, involving neurohumoral and other factors, and its mechanism must be further studied and confirmed. Transcutaneous electroacupuncture (TEA) has been shown to improve gastric

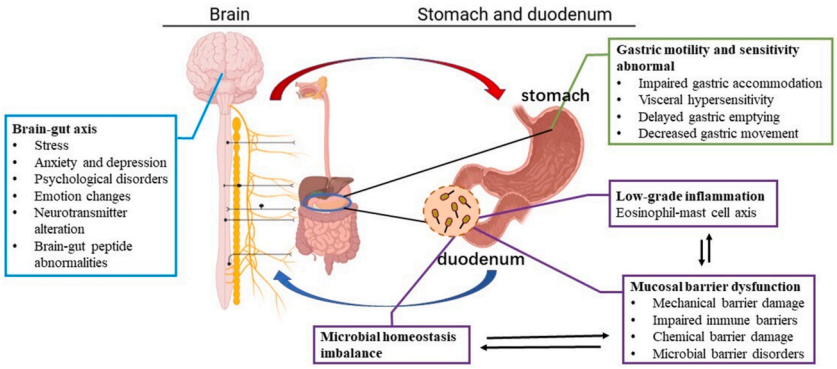

Fig. 1. Potential complex pathophysiology of FD. (1) Gastric motility and sensory disorders are important factors in the occurrence of FD. (2) There is a correlation between low-grade inflammation, microbial imbalance, and mucosal barrier dysfunction in the duodenum. (3) The gastrointestinal tract and brain interact via the brain–gut axis.

accommodation. A double-blind randomized controlled trial assigned 30 patients with PDS to TEA or sham TEA and found that TEA significantly improved initial satiation and maximum tolerance of patients after the intervention. Furthermore, the sympathovagal ratio was reduced, and the expression of interleukin (IL)-6 in the duodenal bulb mucosa was downregulated with TEA treatment [23]. These results highlight that acupuncture may improve gastric accommodation and dyspepsia symptoms by downregulating the expression of IL-6 in the duodenal bulb mucosa via the vagus nerve efferent pathway. Interestingly, TEA could improve impaired gastric accommodation induced by cold drinks in 13 healthy individuals, but no changes in gastric vagus nerve activity were observed [24]. However, TEA combined with breathing significantly increased vagal activity and decreased sympathetic activity [25]. Therefore, a large sample and rigorous trials are needed to further verify the neurohumoral mechanism of acupuncture in regulating gastric accommodation.

2.2. Gastric motility

Receptive relaxation is a special form of gastric motility. The gastric accommodation response and gastric motility disorder are direct physiological abnormalities leading to FD. Gastric motility abnormalities in FD include slow gastric peristalsis, delayed gastric emptying, and impaired gastric accommodation. However, the above pathological changes cannot be completely separated because the symptoms of FD always overlap each other. Acupuncture can improve gastric motility by increasing the gastric emptying rate and small intestinal propulsion rate.

2.2.1. Beneficial effects of acupuncture on interstitial cells of Cajal (ICC)

Movement in the gastrointestinal tract depends on myoelectric activity. As the pacemaker and conductor of slow wave, ICC mainly exist in the muscular layer of the gastrointestinal tract in the form of a reticular structure, and they play a leading role in the formation of the basic electrical rhythm of the gastrointestinal tract, gastric electric conduction, nerve signal conduction, and other physiological functions [26]. Abnormalities of ICC (such as reduction in the number and structure of ICC, decreased expression of gap junction proteins, and damage to neurotransmitter receptors or ion channels in the membrane of ICC) directly or indirectly affect the normal movement of the stomach, resulting in the weakening of gastric motility.

Acupuncture can regulate the expression of ICC number, structure, and function. On the one hand, acupuncture can promote the expression of connexin 43 (Cx43) in the gap junction. First, ICC are involved in the exchange of information, energy, and substance between adjacent cells, and coordinate the transmission of chemical and electrical signals between cells through gap junctions [27]. Second, Cx43 is the most widespread gap junction protein found in the gastrointestinal wall. Decreased expression, deletion, or structural damage of Cx43 can directly inhibit the transduction of electrical signals, thereby affecting the relaxation or contraction function of the gastrointestinal tract, resulting in gastrointestinal motility disorder [28]. Previous studies have shown that the density of Cx43 increases at acupoints, and Cx43 may be an important mediator of acupuncture and meridians [29]. EA increases the level of Cx43 and effectively relieves pathological changes in ICC [30]. On the other hand, acupuncture can inhibit the excessive autophagy of ICC. The ultrastructure of ICC includes abundant mitochondria. Studies have shown that the main reason for the decrease in activity, quantity, and dysfunction of ICC in the stomach is owing to excessive autophagy [31], resulting in insufficient energy supply. In a rat model of FD induced by chronic tail pinch stress, levels of autophagy biomarkers (such as Beclin1 and LC3) were increased in ICC whereas levels of differentiation biomarkers such as c-kit and Stem Cell Factor (SCF) were reduced [31]. As a specific marker of ICC, c-kit combines with SCF to form the c-kit/SCF signaling pathway, which regulates the number and function of ICC. It has been found that the expression of LC3II/LC3I and Beclin1 was increased in FD rats by establishing a model of FD with spleen deficiency syndrome, indicating the existence of excessive autophagy in FD [32]. Other experiments have shown that EA at Zusanli (ST36) can downregulate the protein expression of LC3 II/LC3 I, Beclin 1, phosphorylated (p)-AMP-activated protein kinase (AMPK), and *p*-unc-51 like autophagy activating kinase 1 (ULK1) and upregulate the protein expression of c-kit to promote gastrointestinal motility. Additionally, EA at ST36 can reduce the gastric residual rate and improve the small intestinal propulsion rate in FD rats, which is related to the inhibition of excessive autophagy of ICC by downregulating AMPK/ULK1 signal transduction with acupuncture [33].

Acupuncture can regulate the expression levels of neurotransmitters and ion channels that mediate ICC. There are a large number of neurotransmitter receptors on the cell membrane of ICC, including M2, M3 muscarinic receptors, 5-HT receptors, and vasoactive peptide (VIP-1) receptors [34,35]. All neurotransmitters and humoral factors that can regulate the receptors can affect the structure and function of ICC. Gastric electrical stimulation in diabetic rats increased the level of 5-HT, the expression of 5-HT2B, and the number of ICC in the distal gastric tissue [36], suggesting that electrical stimulation may regulate the proliferation of ICC via the 5-HT/5-HT2B signaling pathway. The ion channels involved in ICC pacing regulate intracellular calcium levels, and the Hyperpolarization-activated Cyclic Nucleotide (HCN) channel [37] acts as a pacemaker channel; its diverse subtypes have different roles in the gastrointestinal tract [38]. HCN1 is the initial ion channel for the rhythmic electrical activity of ICC, and HCN2 can directly affect M receptors in smooth muscle cells or affect the release of acetylcholine (Ach), indirectly acting on ICC to regulate intestinal peristalsis [39]. In this study, moxibustion increased the expression of HCN1 in the gastric antrum, small intestine, and hypothalamic satiety center; activated ICC in the gastrointestinal tract; and improved intestinal peristalsis in FD rats whereas HCN channel inhibitor (ZD7288) prevented the above therapeutic effects [40].

A crucial mechanism of acupuncture in changing gastrointestinal motility function and improving gastrointestinal motility disorder is the beneficial regulation of acupuncture on ICC, including the ultrastructure and number of ICC and certain specific receptors and neurotransmitters on the ICC membranes. Given the complexity of ICC ultrastructure and functions, only the gap junction, autophagy-related, ion channel, and membrane receptor are relatively clear. However, the connection and interaction mechanism between each are indistinct, and the action mechanism of acupuncture in these is also unclear. Until now, there are relatively few studies on the

mechanism of acupuncture in the full function of ICC, in both clinical efficacy and animal experiments.

2.2.2. Bidirectional regulation of vagal-sympathetic nerves via acupuncture

It is well known that autonomic dysfunction plays a necessary role in the development of gastric dysmotility [41]. Patients with FD have been reported to exhibit decreased vagal tone and increased sympathetic activity [42]. Ma's team revealed for the first time the modern neuroanatomical basis of acupuncture regulating the vagus–adrenal pathway [43], which explains the stimulation of specific points and the effect on peripheral nerves. Acupuncture at different points has different regulatory effects on gastric motility. ST36 can promote gastric motility by increasing vagal activation and inhibiting sympathetic activity. Zhongwan (RN12) or RN12 and ST36 can inhibit gastric motility by decreasing vagal activation and increasing sympathetic activity [44]. This reflects the specificity of acupoints. Similarly, electrodes were inserted into the stomach to measure and improve gastric slow waves, and were also implanted into acupoint ST36 for EA. The results showed that EA inhibited the decrease in vagal activity and the increase in sympathetic activity in FD rats. EA decreased the concentration of norepinephrine, increased the level of Ach in the gastric antrum, and improved the slow wave in FD rats [45]. It is suggested that acupuncture at ST36 can activate vagus nerve activity and inhibit sympathetic nerve activity through the vagal cholinergic pathway, which may play a role in delayed gastric emptying.

The traditional vagus nerve, located in the trunk and limbs, as well as the vagus nerve on the body surface, can be stimulated by acupuncture. Recently, transcutaneous auricular vagus nerve stimulation (taVNS) has attracted increasingly more attention. The auricular branch of the vagus nerve is located in the auricle, as the only place where the afferent vagus nerve is distributed on the surface of the human body [46]. Skin electrodes can enhance vagus nerve activity. Noninvasive taVNS is an easy-to-implement neuromodulation method that improves symptoms of both dyspepsia and gastric function, possibly mediated via the enhancement of vagal efferent activity [47].

2.2.3. Acupuncture regulates gastrointestinal hormones and brain-gut peptides

As is well known, the hormones of the brain–gut axis are involved in the regulation of gastrointestinal motility. Studies have focused on prokinetic drugs, including cholinergic agonists, dopamine (DA) agonists, 5-HT4 agonists, ghrelin agonists, and motilin agonists. Acupuncture and moxibustion can regulate some of these gastrointestinal hormones, thereby helping to improve the symptoms related to FD.

Ghrelin is a multifunctional gastrointestinal hormone [48] secreted in rodent and human gastric X/A-like cells [49] that promotes growth hormone release and is an endogenous ligand for the growth hormone secretagogue receptor (GHSR) [50]. Acupuncture can regulate the release of ghrelin and improve gastrointestinal motility disorders [51]. Taking ghrelin as the target, the gastrointestinal propulsion rate of FD rats was significantly accelerated after acupuncture, which may be related to the increased expression of ghrelin after treatment [52]. In that study, EA treatment was performed in FD rats with or without an mammalian target of rapamycin (mTOR) agonist or inhibitor. The results showed that EA promoted significant upregulation of ghrelin expression, increased mRNA levels of AMPK and tuberous sclerosis complex 2 (TSC2), and decreased the mRNA level of Ras homolog enriched in brain (Rheb). Therefore, EA remarkably upregulated ghrelin levels and increased the intestinal propulsion rate and gastric emptying rate by inhibiting AMPK/TSC2/Rheb-mediated mTOR [53]. Although many studies have demonstrated the beneficial effects of ghrelin on FD, the mechanism by which acupuncture regulates ghrelin remains unclear.

Motilin and gastrin play a crucial role in gastrointestinal motility. Motilin belongs to the same family as ghrelin [54], exists in the form of hunger hormone, and has an appetite-stimulating function. In mammals, motilin and its receptors are highly expressed in the gastrointestinal tract and are mainly released from the enteroendocrine Mo cells to stimulate gastric and small intestinal motility [55]. Gastrin is secreted by G cells of the duodenal mucosa and gastric antrum, stimulating gastrointestinal smooth muscle contraction and promoting gastric emptying and gastric acid secretion. The expression levels of motilin and gastrin in the blood of FD rats were significantly lower than those of a normal control group [56]. The results of a study protocol on the effect of lifting and thrusting acupuncture manipulation with different frequencies on the efficacy of FD upper abdominal pain syndrome and serum gastric motion-related hormones were published in a Chinese journal, suggesting that manual acupuncture with faster frequency can significantly regulate the levels of motilin and ghrelin and improve gastrointestinal hormone disorder [57]. In another study, acupuncture at ST36 upregulated motilin and gastrin concentrations and enhanced intestinal peristalsis [58]. Acupuncture increased motilin levels and decreased gastric emptying in a meta-analysis of acupuncture for FD [59]. Notably, motilin reduced proximal gastric volume in patients with FD compared with healthy individuals, and no difference was observed in gastric motility [60]. This leads us to question whether motilin expression is specific in FD patients.

Neuropeptides such as ghrelin, neuropeptide Y (NPY), glucagon-like peptide-1 (GLP-1), and calcitonin gene-related peptide (CGRP) have been extensively studied in FD. In a study assessing neuroendocrine function, EA was observed to modulate serum ghrelin, GLP-1, and CGRP levels while improving dyspeptic symptoms [61]. After 36 weeks of transcutaneous neuromodulation of Neiguan (PC6) and ST36 in FD patients, it was found that the levels of ghrelin and NPY were significantly increased, vasoactive intestinal peptide (VIP) was decreased, and the proportion of gastric electric rhythm disorder before and after meals was reduced. Furthermore, the gastric accommodation and gastric emptying rates were improved after the combination of the two points [62]. Our previous studies also showed that EA promotes gastrointestinal motility and accelerates gastric emptying by increasing the level of gastrointestinal hormones such as IGF-1, motilin, gastrin, and SCF [63,64].

Although acupuncture can regulate the secretion of gastrointestinal hormones, which usually act as downstream substrates, no favorable molecular mechanism has been proposed. Further studies are needed to examine the correlation between gastrointestinal hormones and to confirm the effect of acupuncture on FD.

2.3. Visceral hypersensitivity

VH is one of the main physiological and pathological bases of FD. There is an evidence that FD patients have changes in visceral function [65]. Meanwhile, increased visceral sensitivity in patients with FD is associated with postprandial epigastric pain, belching, and weight loss and is positively correlated with the severity of FD symptoms [66]. VH is induced by a variety of factors, including mechanical, chemical, temperature, and psychosocial factors. There are many mechanosensitive cells in the gastrointestinal tract, such as enterochromaffin cells (ECs), enteric neurons, smooth muscle cells, and ICC. Among them, ECs are important neuroendocrine cells in the intestinal mucosa that play an important role in synthesizing and secreting 5-HT and regulating gastrointestinal motility, and especially in visceral sensation [67]. Approximately 95 % of 5-HT in humans is secreted by ECs, and more than 90 % of 5-HT is stored in ECs [68]. 5-HT mediates the secretory, motility, and sensory functions of the gastrointestinal tract by acting on various receptors expressed on smooth muscle, intestinal neurons, intestinal cells, and immune cells [69,70]. 5-HT1, 5-HT3, 5-HT4, and 5-HT7 receptors have been implicated in the regulation of visceral sensitivity [71,72]. The mechanism of mast cells (MCs) and visceral sensitivity is not fully understood, which may be related to the change in nerve potential by 5-HT and histamine, increasing the release of substance P and CGRP from nerve terminals, inducing central and peripheral sensitization [73]. In conclusion, a neuroendocrine–immune network including neurons (enteric nervous system), endocrine (ECs), and immune (eosinophils, MCs) elements is involved in VH [74,75].

It is noteworthy that the development of VH is also influenced by psychological stress in the brain centers [76]. The limbic system is a central site closely related to VH induced by mental stress, which can directly cause abnormal activation of the hypothalamus and anterior cingulate gyrus under mental stimulation [77]. Corticotropin-releasing factor (CRF) is a key factor mediating central and peripheral VH. Based on the theory of brain–gut interaction, the occurrence and development of FD is closely related to the brain and the gut [78]. Studies have shown that stress and negative emotional responses can lead to alterations in visceral sensory and motor functions [79]. There are different brain response areas in the central regulatory response to acupuncture. Immediate changes on fMRI in 48 patients with FD after acupuncture at ST36 showed that fMRI signals of the right insula, right postcentral gyrus (PG), and right supralimbic gyrus (SG) increased after acupuncture [80]. Most of these regions belong to the limbic–paralimbic system and homeostatic afferent processing network.

Above all, the regulation of gastric motility and sensory disorders by acupuncture involves neuromodulation and humoral regulation. The functions of the stomach and intestine cannot be completely separated, especially in elucidating the mechanisms related to gastrointestinal motility (Fig. 2). Acupuncture and moxibustion have a multi-target regulatory effect that can not only regulate the gastrointestinal smooth muscle itself but also regulate the related hormones, neurotransmitters, and smooth muscle cell activity through nervous and endocrine regulation, thereby regulating gastrointestinal motility and sensation.

3. Potential targets of acupuncture on the duodenum

Pathologic changes centered on duodenal mucosal alterations, including impaired mucosal barrier function and low-grade inflammation, are closely related to the pathogenesis of FD [81]. A growing number of evidence suggests that there is damage to the structure and function of the duodenal barrier in FD, which leads to increased mucosal permeability, and invasion of some pathogenic microorganisms or toxins, causing local inflammatory reactions. And persistent low-grade inflammation causing a decrease in the expression of tight junction proteins, which exacerbates the damage to the mucosal barrier, and so on, forming a vicious circle

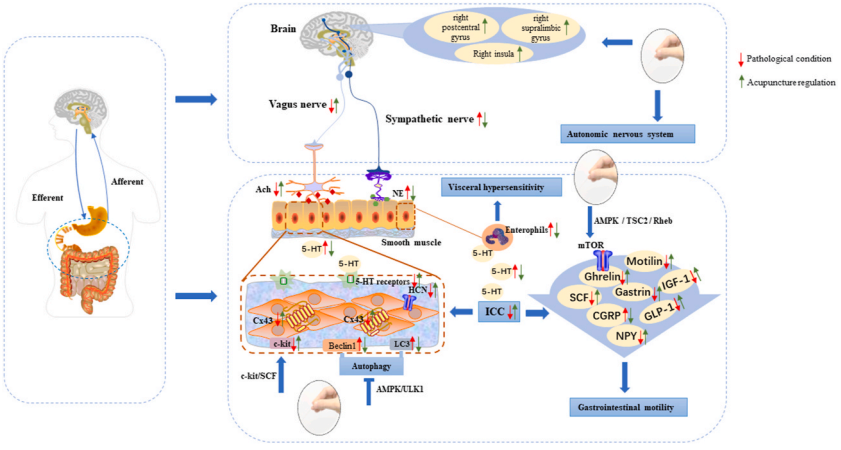

Fig. 2. Mechanisms of gastrointestinal motility disorder. (1) Gastrointestinal motility depends on myoelectric conduction. Taking the ICC as the core, acupuncture can directly regulate the number and structure of ICC, inhibit excessive autophagy to ensure ICC function, and maintain ICC activity through the expression of the membrane receptor and ion channel. (2) Acupuncture regulates the release of gastrointestinal hormones and brain–gut peptides. (3) Acupuncture activates vagus nerve activity and inhibits sympathetic nerve activity to regulate autonomic nervous system, and enhances fMRI signals in some brain regions. (4) Acupuncture inhibits visceral hypersensitivity by reducing 5-HT levels. ↑: increase or activate, ↓: decrease or inhibit.

[82]. In addition, microbiota disruption and emotional changes such as stress can also exacerbate the clinical symptoms of FD [83,84]. Focusing on the duodenum, the potential mechanisms of acupuncture in treating FD are elaborated, based on low-grade inflammation, mucosal barrier damage and microbial homeostasis dysregulation in FD.

3.1. Low-grade inflammation of duodenal

In recent years, intestinal inflammation has gradually become one of the important pathogenesis of FD, and a large number of studies have confirmed the existence of low-grade inflammation in duodenal mucosa [85,86]. Especially when Talley et al. first reported that duodenal eosinophilia was closely related to FD [87]. And in a prospective observational study, the counts of duodenal eosinophils (EOS) were increased in FD patients [86], which was strongly positively correlated with PDS subtype [85]. At the same time, the MCs in duodenal are also significantly increased [88], so these two cells may play a key role in functional dyspepsia through various immune responses. MCs and EOS are usually co-dependent. They participate in the mucosal system immune response and play a defense role in the healthy host. EOS are activated by allergy or post-infection inflammation, releasing major basic protein (MBP) and other soluble mediators (such as CRH), which can trigger mast cell degranulation and release of inflammatory cytokines [89]. EOS, MCs and degranulation were significantly increased in FD compared with healthy controls, and MCs and MCs degranulation were more prominent [90]. Interestingly, in a meta-analysis involving 1108 FD patients and 893 controls, duodenal EOS and MCs were significantly increased in FD patients, duodenal EOS degranulation was also significantly increased, whereas MC degranulation was unchanged, and no difference in EOS and MCs were found when comparing FD subtypes [91]. This may be related to the lack of standardization of cell counts and a diagnostic threshold for FD duodenal EOS and MCs, and the low quality of evidence, which should be interpreted with caution. Notably, more studies have found that both EOS and MCs were increased in FD patients [88,90]. Although EOS and MCs may be important cells in the pathogenesis of FD, the specific molecular mechanisms of these two cells in FD need further study. Based on the theory of the duodenal eosinophil-mast cell axis [89], targeted therapies for the duodenum may emerge in the future.

MCs can be used as a target for acupuncture and moxibustion. In 1977, Professor Song Jimei from Liaoning College of Traditional Chinese Medicine first proposed that mast cells are related to acupoints [92]. The relationship between MCs and the human acupuncture system is very close [93]. There was significant difference in MCs between acupoint and non-acupoint. Studies have shown a higher density of mast cells at acupuncture points [94]. Acupuncture at ST36 can increase the degranulation of mast cells [95]. The beneficial effects of MCs activation mediated by acupuncture analgesia may involve the activation of ion-selective channels [96] and signal transduction including adenosine triphosphate (ATP) [97], histamine, and 5-HT. In addition, acupuncture reduced the number of MCs and down-regulated TLR4, IL-1β and IL-8 released by MCs in colonic, reducing the gastrointestinal inflammatory reaction [98]. Based on the target of MCs, we hypothesized that acupuncture and moxibustion may improve low-grade duodenal inflammation by regulating eosinophil-mast cell axis, which needs the further research and demonstration to explore a new way to relieve FD.

In addition, some studies have found that low-grade inflammation of the duodenum in FD patients may be related to previous infection. Among the 136 FD patients recruited, 35 of whom were diagnosed to have prodromal symptoms of acute gastroenteritis, and the rest were divided into EPS and PDS according to FD manifestations [99]. The results showed that the number of EOS in duodenum of FD patients after infection was significantly increased compared with that of non-infected ones and healthy controls. *H. pylori* (HP) infection is of additional concern, although the relationship between HP and FD is controversial. In any case, HP does increase the occurrence of FD [100]. And HP infection is considered to be one of the causes of FD [101]. The *Kyoto Consensus* [102] and Rome IV criteria defined it as "H. pylori-associated dyspepsia" and specify that HP eradication should be done first for FD with HP. And HP eradication therapy can improve dyspeptic symptoms in some FD patients. The efficacy of treatment was seen in all subtypes of FD and was more pronounced in Asian patients than in Western [103,104]. The quadruple therapy recommended in western medicine can achieve good results in a short term, but it will promote excessive growth of bacteria and poor prognosis in the long-term. Some scholars in China have been exploring the influence of traditional Chinese medicine on HP. Acupuncture and moxibustion at multiple targets can improve the negative conversion rate of HP and reduce adverse reactions [105]. However, multi-center and large-sample clinical data are still needed to provide favorable demonstration.

3.2. Barrier function of duodenal mucosa

The damage of intestinal mucosal barrier, especially the mechanical barrier, is one of the important pathological bases of gastrointestinal diseases [106]. As the central part of the mechanical barrier, epithelial cells are divided into tight junctions (TJ), gap junctions, adhesive junctions and desmosomal junctions, among which TJ proteins including zonula occludens-1 (ZO-1), occludin and claudin family are the most importan [107]. The Ussing Chamber trial [108] showed that patients with FD had increased duodenal mucosal permeability and decreased expression of TJ (ZO-1, occludin), adhesive junctions (β-catenin, E-cadherin), and desmosomes (Desmoglein-2). In a controlled clinical study investigating impaired gastrointestinal mucosal barrier function in patients with FD, the results showed that duodenal mucosal electrical impedance (MI) in FD was significantly lower than that in symptomatic and asymptomatic controls [109]. Interestingly, there was no significant difference in gastric MI. Meanwhile, duodenal MI values were positively correlated with ZO-1 [109], which suggesting the change of duodenal mucosal barrier function in FD patients may be related to the decrease of ZO-1. In addition, low-grade inflammation in the duodenum is strongly correlated with intestinal mucosal barrier integrity [108]. Damage to the mechanical barrier of the mucosa reduces the transmembrane resistance of the intestinal epithelium, and increases the permeability of the intestinal tract, which turning the intestinal mucosa into a "leaky membrane," followed by

intestinal leakage [110]. Some harmful substances, such as toxins and bacteria, cause immune activation and inflammation in the intestinal tract, which subsequently lead to changes in some inflammatory factors like IL-6, IL-1β and tumor necrosis factor alpha (TNF-α). While the negative feedback of the stimulation of inflammation aggravates the damage to the structure and function of the intestinal mucosa [111]. The duodenum of FD patients is accompanied by mild inflammation, which leads to the decreased expression of intestinal epithelial tight junctions occludin, claudin-1 and ZO-1 protein and mRNA, and eventually resulting in the dysfunction of intestinal mucosal barrier [112]. The findings of Wang et al. [113] that MCs degranulation decreases the expression of tight junction proteins (claudin-8, ZO-1 and occludin), and the application of Protease-activated receptor 2 (PAR-2) antagonists and inhibitors of the extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway significantly reduced the effect of MCs degranulation on TJ proteins, suggesting that the PAR-2 and ERK1/2 signaling pathways may disrupt the intestinal barrier by interfering with the expression of tight junction proteins through MCs-mediated low-grade inflammation. Animal experiments also showed that the increased intestinal mucosal permeability of FD rats is caused by the decrease of claudin-1, which due to the abnormal increase of TNF-α and INF-γ in duodenum [114].

Acupuncture can repair intestinal mucosal injury and barrier function by inhibiting inflammation and regulating the expression of TJ proteins [115]. In animal experiments, acupuncture can effectively improve the intestinal mucosal barrier function by inhibiting colonic inflammation and increasing the expression of occludin and ZO-1 in an obese rat model research [115] EA and manual acupuncture were respectively used to treat FD rats for 14 days, and found that both of them could reduce the increased levels of IL-6 and TNF-α in serum and TLR4, Myd88 and NF-κB-p65 in duodenum, and increase the expressions of ZO-1 and occludin protein and mRNA [116]. And the gap between duodenal epithelial cells was clear and the villi were arranged in order under electron microscope, which indicated that acupuncture could improve and repair the mucosal barrier. Another study showed that EA can inhibit the activation of duodenal mast cells, increase the expression of claudin-1 and JAM-1, and reduce FD rats low-grade inflammation and damage to the intestinal mucosal barrier [117]. Interestingly, EA stimulation of lower limbs (ST36, ST37 and ST39) or abdominal acupoints (ST25, CV4 and CV12) was performed on 48 FD model rats, and the results showed that acupoints on lower limbs could improve duodenal claudin-3 and ZO-1, but only ST36 inhibited the expression of eosinophil major basic protein (EMBP) and restored the levels of occludin-1 (a tight junction protein) [118]. This indicates that acupoints have specific function.

3.3. Microbial homeostasis: a new possible treatment point

The correlation between duodenal microbial changes and FD [119] is the focus of current research. It is well known that the intestinal symbiotic microbiota plays a necessary role in maintaining the host–microbial ecosystem and the integrity of the epithelial cell barrier. The microbial imbalance caused by a decrease in the number of beneficial bacteria and an increase in pathogenic bacteria damages the intestinal microbial barrier, destroying intestinal mucosal TJs and decreasing the expression of claudin-1, occludin, and ZO-1 [120,121]. As a result, increased permeability of the mucosa and invasion by pathogenic bacteria and endotoxins into the intestine cause damage to the immune system and inflammation and promote the release of IL-6, IL-1β, and TNF-α, which further aggravates the mucosal barrier and permeability, creating a vicious cycle [122,123]. In addition, abnormal infiltration of metabolites of intestinal microbiota, such as short-chain fatty acids (SCFAs) like acetate, can also induce the release of inflammatory factors, and persistent low-grade inflammation is an important factor in the occurrence of FD [124]. Diversity structure and composition of microbial species in the duodenal mucosa and other parts of the gastrointestinal tract are not exactly the same [125]. And the duodenal microbiome is dominated by the genus *streptococcus*, with lower levels of *Prevotella*, *Wetheria*, and *Neisseria* [126]. Clinical studies have demonstrated that the concentration of *Streptococcus* in the duodenal mucosa of FD patients is increased, but that of *Prevotella*, *Veillonella*, and *Actinomyces* is decreased, as well as new strains of *Corynebacteria* and *Carnobacillus* on the mucosa [127]. Similarly, animal experiments have shown that the number and proportion of intestinal microbiota in FD rats are changed, such as a significantly decrease in SCFAs-producing bacteria (including *Allobaculum*, *Clostridium* and *Adlercreutzia*) and the sulfate-reducing bacteria Desulfovibrionaceae (including *Desulfovibrio*), rather an increase in *Verrucomicrobia*, *Deferribacteres* and some other bacteria [128].

Acupuncture can improve the ecological balance of microorganisms by regulating the number and proportion of microbiota. EA can increase the alpha and beta diversity of gut microbiota in the duodenum, as well as the abundance of beneficial bacteria at phylum and genus levels, this effect may be mediated by inhibition of the NF-κB p65/NLRP3 pyroptosis pathway [129]. EA at LI10 and ST36 can increase the abundance of *Bacteroides* in the stomach and decrease the count of Firmicutes in the stomach and duodenum of rats with peptic ulcer [130]. However, this is not restricted to the duodenum. It was found that EA could significantly increase the diversity and abundance of intestinal microbiota in mice with irritable bowel syndrome (IBS), enhance the colonization ability of probiotics and weaken the number of pathogenic bacteria, and transform probiotics to the normal direction [131]. Moxibustion can alleviate a decrease in the levels of *Lactobacillus* and *Bifidobacterium* and an increase in *Clostridium* in animals with spinal cord injury [132]. EA helped improve signs of leakage in rats with stress urinary incontinence by enriching the proportion of *Blautia* [133]. EA also contributed to ameliorating abdominal obesity and preventing metabolic disorders in rats induced with a high-fat diet by decreasing the Firmicutes*/Bacteroides* ratio and increasing the abundance of *Prevotella 9* [134]. In a randomized controlled trial of acupuncture in the treatment of mild to moderate Crohn's disease, acupuncture effectively helped to restore the intestinal microbial balance and relieved adverse symptoms by increasing the abundance of *Faecalibacterium prausnitzii* and *Roseburia faecis* and reducing inflammation [135].

FD is usually associated with negative emotions such as anxiety or depression, which have been found in both humans and animals. There is a significant correlation between emotions and gut microbiota [136]. Studies have shown that the abundance of intestinal microbes was decreased in a rat model of depression, which could be reversed with acupuncture. Acupuncture also regulated the imbalance of *Bacteroides/Firmicutes* and reduced the relative abundance ratio [137]. Furthermore, acupuncture improved the levels of

DA and 5-HT in both serum and the hippocampus and increased the expression of brain-derived neurotrophic factor (BDNF) and astrocytes in the hippocampus. Therefore, acupuncture can improve depression through the bacteria–gut–brain axis [138]. There is an interaction among microbiota, the intestines, and the brain. An imbalance of the microbiota activates inflammation and causes impairment of the intestinal barrier, gastrointestinal motility disorder, and abnormal intestinal secretion, which is further transmitted to the brain via intestinal peptides, nerves, and cytokines and then fed back to the intestinal tract and microbiota. Acupuncture can interfere with the brain–gut axis and restore a beneficial circle. A growing body of evidence supports that dysregulation of the microbiota–gut–brain axis is closely related to the progression of neurodegenerative diseases [139]. The mechanism by which EA effectively alleviated cognitive dysfunction in a rat model of aging may be related to inhibition of the Toll-like receptor 4 (TLR4)/nuclear factor (NF)-κB pathway; that is, EA could downregulate the levels of TLR4, P–NF-κB p65, TNF-α, IL-6, and IL-1β and could upregulate the DNA abundance of *Lactobacillus* and *Bifidobacterium* [140]. Thus, the brain–gut–microbiota axis plays a vital role in regulating chronic inflammation and restoring balance to the intestinal microbiota.

Another key factor affecting the bacteria–gut–brain axis is microbial metabolites. When Kelly et al. transplanted the intestinal microbiota of depressed patients into the intestines of sterile rats, they found that the ratio of kynurenine to tryptophan in plasma was increased, and the neurobehavior of rats was changed [141]. The intestinal microbiota is known to be involved in the metabolism of carbohydrates, proteins, amino acids, lipids, vitamins, and drugs. SCFAs (acetate, propionate, and butyrate) are among the major metabolites of microorganisms, mainly produced from the fermentation of dietary fiber by intestinal anaerobes. SCFAs have been shown to not only cross the blood–brain barrier [142] and maintain the integrity of the blood–brain barrier by promoting TJs [143], but they also modulate the immune response and inflammation of the intestinal epithelium and protect the intestinal mucosa [144]. The gut microbiota is involved in the synthesis of a variety of neurotransmitters such as gamma-aminobutyric acid (GABA), 5-HT, DA, Ach, and other neuroactive molecules synthesized by the microbiota [145–147], which in turn indirectly influence the abundance of the microbiota [148]. Microbial metabolites also stimulate enterochromaffin cells to regulate the metabolism of 5-HT [149]. In recent years, studies based on metabolomics have found that acupuncture has a significant regulatory effect on metabolites in the digestive system [150,151], cardiovascular and cerebrovascular systems [152], and immune system [153].

Although the occurrence of FD is closely related to changes in the gut microbiota, the specific mechanism is not clear. As a therapeutic target, the intestinal microbiota is promising, and acupuncture is beneficial, as discussed above. First, acupuncture can regulate the abundance of gut microbiota by altering the number and proportion of bacteria. Second, acupuncture can repair the intestinal barrier by reducing central and peripheral inflammation, improving mucosal permeability, and inhibiting the transfer of microbiota. Finally, acupuncture can regulate microbial metabolism, which may be related to the brain–gut–bacteria axis (Fig. 3). Therefore, it is important to clarify the mechanism of acupuncture of intestinal microecology, the bacterial–membrane barrier, and the bacteria–gut–brain axis in FD on a pathological basis.

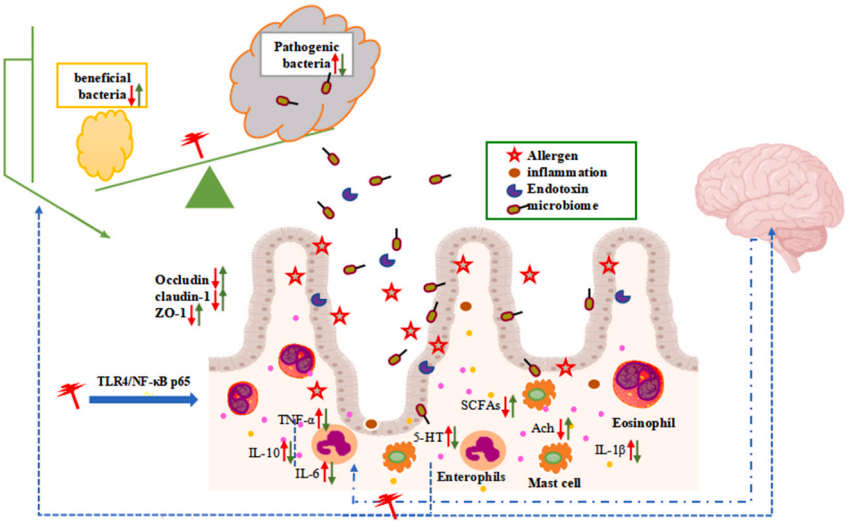

Fig. 3. Acupuncture regulates the duodenal mechanism. Duodenal mucosal barrier function is closely related to chemistry, immunity, and microorganisms. (1) Acupuncture improves the imbalance of microorganisms and inhibits central and peripheral inflammation, thereby restoring mucosal permeability. (2) Acupuncture regulates the level of tight junction proteins to restore the integrity of the mucosal barrier. (3) Acupuncture coordinates the synthesis and secretion of multiple neurotransmitters and plays an important role in the information exchange of the bacteria–gut–brain axis.

4. Discussion

4.1. Broad-spectrum and acupoint-specific acupuncture

As integral elements of traditional Chinese medicine (TCM), acupuncture and moxibustion have a history spanning more than 2000 years. Acupuncture is guided by the theory of meridians. Meridians are described in ancient Chinese medical books; "Meridians belong to the zang-fu organs internally and connect to the extremities and joints externally," having the function of communicating across the entire body from interior to exterior, upward and downward [154]. Therefore, with the stimulation of meridians, acupuncture and moxibustion can achieve the effect of dredging the meridians and regulating collaterals as well as balancing yin and yang. This is the overall regulation of acupuncture in the body. It is well known that acupuncture has multi-target, multi-directional, and multi-level regulatory effects, which involve the integration and regulation of acupuncture signals and effects in different dimensions, thus having an overall coordinating effect. In the treatment of FD with acupuncture and moxibustion, acupuncture and moxibustion have a certain regulatory effect on movement and sensation in the stomach and duodenum, which can not only regulate the levels of related factors in the neural–humoral–endocrine network but can also coordinate and repair chemical, immune, and microbial homeostasis related to the intestinal barrier. This reflects the universality of acupuncture, which is also specific at the same time. The basis of the acupuncture effect is the specificity of the structure and function of meridians and acupoints. The specificity of acupoints does not refer to the effectiveness of acupoints but the difference in the "quality" of intrinsic effects of acupoints (such as the effects of presence or absence, activation or inhibition). As is known at present, the regulating effects of acupuncture at ST36 and RN12 on autonomic nerves are different [44]; thus, the modulation of organs in the body is discrepant.

4.2. Multiple targets and complex regulation of acupuncture in FD pathology

Efficacy in the treatment of FD remains unsatisfactory due to its complex pathophysiology. Thus, the search for complementary and alternative therapies [155] has become important. Based on the pathophysiology of FD, previous studies have mostly focused on abnormalities of gastric motor and sensory function, with duodenal lesions gradually receiving greater attention. We comprehensively discussed the possible mechanism of acupuncture in the stomach and duodenum based on the pathophysiology of FD.

First, gastrointestinal motility disorders include delayed gastric emptying, impaired gastric regulation, and abnormal gastric electrical rhythms. Current guidelines [156] recommend the use of prokinetic drugs and acid inhibitors, but their efficacy is unsatisfactory. Long-term use of drugs can cause adverse reactions [157]. Once the most frequently used drug for FD, cisapride was discontinued because of a risk of sudden death. As a traditional and effective non-drug therapy, it is generally accepted that acupuncture and moxibustion can regulate the autonomic nervous system. On the one hand, acupuncture and moxibustion can regulate the number and activity of ICC in gastrointestinal smooth muscle and reduce excessive autophagy to maintain the function of ICC and produce normal gastric electrical rhythm and promote gastrointestinal motility. On the other hand, acupuncture can accelerate gastric emptying and improve gastric motility by improving the synthesis and release of gastrointestinal hormones and peptides and adjusting the adaptability of the stomach.

Second, low-grade duodenal inflammation and VH are also the main pathologies in FD, and there is an internal correlation between them. The EOS–MC axis plays a key role in low-grade inflammation, and both EOS and MCs are also involved in VH. Here, MCs seem to be key elements in the communication bridge. Acupuncture and moxibustion have regulatory effects on MCs and degranulation. The density of MCs varies locally at acupoints [94]; mechanical stimulation with acupuncture can reduce the number of MCs and decrease the release of 5-HT, histamine, and other active substances to reduce visceral sensitivity and inflammation. FD is defined as a functional disorder of brain–gut interaction [158]. 5-HT is an important brain–gut peptide. Acupuncture can regulate the level of 5-HT and the expression of related receptors.

Third, the structural and functional integrity of the duodenal barrier is closely related to microbial homeostasis, which is considered to play an important role in the pathogenesis of FD. An increasing number of studies have found that microbiota have a crucial part in brain–gut interaction based on the theory of the gut–brain axis. A complex neurohumoral interaction network [159] involving the gut microbiota, bacterial metabolites, intestinal nervous system, brain–gut peptide, and central nervous system has gradually received increasing attention. Acupuncture can directly or indirectly regulate the type, quantity, and proportion of microbes; increase beneficial bacteria; and decrease pathogenic bacteria. Acupuncture restores balance to the intestinal microbes by regulating inflammation and can regulate the expression of TJ proteins and restore integrity of the structure and function of the intestinal mucosal barrier. The mechanism of acupuncture in treating FD is complex, just as the pathological basis of FD is complex and heterogeneous. Therefore, this mechanism remains to be elucidated.

In addition, A recent study showed that duodenal acidification can resulted in lower intragastric pressure, increased duodenal permeability and lower protein expression of claudin-3, which inhibit gastroduodenal motor reflex and impair duodenal epithelial barrier function [160]. Keely S elaborated that the loss or imbalance of bile-acid-microbiota-epithelial homeostasis may be an important process driving the occurrence and development of FD [161]. In FD patients, acid suppression therapy in the eradication of the HP case can effectively cure or improve the symptoms of FD [162,163]. EA at ST 36 can increase gastric acid secretion in rats by stimulating the somatic vagus nerve [164]. The contents of gastrointestinal hormones (motilin, gastrin) and neuropeptides (CCK) are closely related to gastric acid secretion and the gallbladder contraction. Acupuncture can indirectly regulate gastric acid and bile secretion, improve gastrointestinal motility by regulating the release of these brain-gut peptides [145].

5. Conclusions and perspectives

Current studies on the mechanism of acupuncture in the treatment of FD are insufficient. Based on the published literature, we focused on the main lesion sites of FD (stomach and duodenum) from the perspective of the potential pathophysiology of FD, and elucidated the targets and possible potential approaches of acupuncture treatment of FD. We found that acupuncture can improve gastric motility significantly, and its pathway is closely related to ICC structure and function. Taking the ICC as the core, acupuncture can directly regulate the number and structure of ICC, inhibit excessive autophagy to ensure ICC function, and maintain ICC activity through the expression of the membrane receptor and ion channel. At the same time, acupuncture can regulate gastrointestinal hormone levels and has a beneficial regulation effect on autonomic nervous system. In addition, acupuncture can inhibit inflammatory response and improve the type and quantity of intestinal microorganisms and their metabolites, which can repair the structure and function of duodenal barrier. At present, using proteomics, transcriptomics, metabolomics and other methods to observe the expression of related proteins, mRNA and metabolites can help us further explore the mechanism of acupuncture treatment of FD. In the future, our team plans to comprehensively explore the mechanism of acupuncture treatment of FD from the perspective of duodenal microbiome and membrane balance reconstruction by combining various technical advantages, so as to provide practical and reliable experimental basis for acupuncture treatment of FD.

Data availability statement

This research was not applicable, no data was used for the research described in the article.

Ethical statement

This review includes no clinial or animal experimental design. Therefore, ethics approvement is not applicable in this manuscript.

Funding

This research was supported by “National Natural Science Foundation of China (No. 82274661)”.

CRediT authorship contribution statement

Hongxiu Chen: Writing – original draft, Visualization. **Min He:** Writing – review & editing. **Jiazhen Cao:** Writing – review & editing, Visualization. **Yifan Zhang:** Visualization, Data curation. **Ying Zhou:** Data curation. **Qianhui Yu:** Data curation. **Anjie Wang:** Data curation. **Jing Xuan:** Writing – review & editing. **Tie Li:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank LetPub (www.letpub.com) for its linguistic assistance during the preparation of this manuscript.

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