The role of lithium in gastrointestinal health and disease

Min Wen[1], Guoyou Gou[1], Haiyan Zhao[1], Rui Cai[1], Chunyan Li[1], Youjia Liu[1], Fang Wang[1], Ya Deng[1], Xingyi Mu[1], Xianmin Lu[1], Chen Luo[1], Qian Du[1], Jingyu XU[1], and Rui Xie[1]

[1]Zunyi Medical University

May 16, 2024

Abstract

Lithium salt as a common drug in the clinical treatment of bipolar disorder, its application range is very wide. Lithium ions have many physiological functions, such as improving hematopoietic function, regulating the nervous system, improving heart function, antiviral, immune regulation, and neuroprotective effects. Lithium also has numerous pharmacological effects. For example, it can be used as an emotional stabilizer and has anti-inflammatory effects in dermatology. It also has protective effects against various neurological diseases, leukopenia, hepatitis, pancreatic islet cells, etc. After oral absorption of lithium salt, it can regulate gastrointestinal epithelial ion transport, affect intestinal absorption and secretion, and repair mucosal damage to promote wound healing. In this review, we review in detail the current status of lithium on gastrointestinal physiology and pathology. Based on the multiple regulatory effects of lithium salts on the gastrointestinal tract, we expect to find new drug targets to better treat gastrointestinal diseases.

The role of lithium in gastrointestinal health and disease

Guoyou Gou1†, Min Wen1†, Haiyan Zhao1 , Rui Cai1，Chunyan Li1, Youjia Liu1, Fang Wang1, Ya Deng1, Xingyi Mu1, Xianmin Lu1,Chen Luo1,Qian Du1, Jingyu Xu[1#] ,Rui Xie[1#]

Department of Gastroenterology, Digestive Disease Hospital, Affiliated Hospital of Zunyi Medical University, Zunyi, China.

† Equal contribution

#Correspondence should be addressed to:
Prof. Rui Xie, MD, Ph. D, Department of Gastroenterology, Zunyi Medical University, China. Email: xr19841029@aliyun.com
Tel: +86 15120390646
Prof. Jingyu Xu, MD, Ph.D., Department of Gastroenterology, Zunyi Medical University, China. Email: xujingyu_gzzy@126.com
Tel: +86 13765298886; Fax: +86 851 28609205

Abstract: Lithium salt as a common drug in the clinical treatment of bipolar disorder, its application range is very wide. Lithium ions have many physiological functions, such as improving hematopoietic function, regulating the nervous system, improving heart function, antiviral, immune regulation, and neuroprotective effects. Lithium also has numerous pharmacological effects. For example, it can be used as an emotional stabilizer and has anti-inflammatory effects in dermatology. It also has protective effects against various neurological diseases, leukopenia, hepatitis, pancreatic islet cells, etc. After oral absorption of lithium salt, it can regulate gastrointestinal epithelial ion transport, affect intestinal absorption and secretion, and repair mucosal damage to promote wound healing. In this review, we review in detail the current status of lithium on gastrointestinal physiology and pathology. Based on the multiple regulatory effects of lithium salts on the gastrointestinal tract, we expect to find new drug targets to better treat gastrointestinal diseases.

Keywords: Lithium, Gastrointestinal tract, physiology, pathology, gastrointestinal diseases

1. Introduction

Lithium (Li) ranks third in the periodic table and belongs to Group IA, with an atomic weight of 6.941 and a specific gravity of 0.534, making it the lightest metal. Abbreviations of the review in **Table.(1).** Lithium, which is in the same alkali metal group as sodium and potassium, is a monovalent positive ion, similar in many respects to Na^+ and K^+, but its higher charge/radius ratio also tends to be similar to ions of some Group IIA elements, especially Mg^{2+} and Ca^{2+}[1] .There is already plenty of evidence that lithium ions play important physiological functions. Including ① as a neutrophil stimulant, improve hematopoietic function, improve human immune function[2]. ② Regulate central nervous activity, play the role of sedation,

sedation, control nervous disorders[3]. ③ As an alternative to sodium, it prevents cardiovascular disease. It can increase the content of lithium in plasma or red blood cells, reduce the incidence of cardiovascular disease and improve heart function. Study on the relationship between trace element lithium and some cardiovascular diseases[4] ④ Antiviral, immunomodulatory and neuroprotective effects[5].

In addition to physiological functions, lithium is also involved in the pathogenesis of many diseases. So far, many literatures have reported that lithium (lithium carbonate) as a mood stabilizer is the first-line drug for the treatment of bipolar disorder, and lithium can also reduce the risk of suicide in patients with major depression and play a role in suicide prevention[6, 7]. In dermatology, lithium salts (lithium gluconate, lithium succinate) act as an anti-inflammatory therapy by inhibiting adenylate cyclase, resulting in reduced cycloAMP formation, neutrophils and T lymphocytes involved in the inflammatory response. Lithium salts (lithium chloride and lithium carbonate) protect islet beta cells from damage by reducing hyperglycemia, hypereating, polydipsia, and weight loss[8]. In addition, lithium also shows a certain protective effect in acute nerve injury, chronic degenerative diseases, neurological diseases such as Alzheimer's disease, as well as in the treatment of leukopenia, hepatitis, and some kidney diseases[9]. Lithium action mechanism contain: ① Inhibition of second messenger enzymes (eg. Inositole monophosphate); ② Modulation of G proteins; ③ Interaction at various sites with downstream signal transduction cascades (eg. Inhibition of GSK3, PKC).

Nowadays, a lot of scientific research has been conducted on the mechanism of action of lithium as a psychotropic drug on the central nervous system, especially bipolar disorder. However, there is a lack of in-depth understanding of how lithium affects gastrointestinal function when taken orally, so it is essential to clarify in detail what role lithium plays in gastrointestinal health and disease. In the digestive system, lithium can inhibit salivary secretion, regulate epithelial ion transport and bicarbonate secretion, inhibit gastrointestinal smooth muscle contraction, and cause endothelium-dependent relaxation. However, lithium is also closely associated with the pathogenesis of gastrointestinal diseases. Examples include chronic secretory diarrhea, visceral hypersensitivity, hepatic ischemia/reperfusion, colitis and colon cancer. In this review, we use lithium ion and various gastrointestinal physiology and diseases as keywords to search relevant literature, explore the possible mechanism of action of lithium ion and its potential new targets for treatment of gastrointestinal diseases.

2. Lithium ion and gastrointestinal function

2.1 The regulatory effect of lithium ion on gastrointestinal epithelial anion secretion

Intestinal epithelial ion transport is an important physiological process in the human gastrointestinal tract. In addition to absorbing electrolytes, the intestinal epithelium can also secrete anions (such as $HCO3^-$, Cl^-) to provide power for body fluid transport and maintain body fluid balance[10]. As we all know, the secretion of chloride ions is closely related to intestinal water balance, diarrhea and constipation. The secretion of intestinal bicarbonate plays an important role in intestinal mucosal protection and acid-base balance[11-14]. Intestinal epithelial anion secretion is controlled by a variety of neurohumoral factors, such as ACh, PGE_2 and 5-HT[15]. PGE_2 plays a protective role in gastrointestinal tract by stimulating the secretion of $HCO3^-$ and Cl^- [16].As mentioned above, lithium ions can stimulate the production of endocannelprostaglandins, so can lithium ions regulate gastrointestinal anion secretion through PGE_2? It has been previously reported that lithium chloride is a potent gastric antisecretory and protective agent, and this protective effect is affected by the inhibition of gastric acid secretion independent of endogenous prostaglandins[17]. This contradictory statement needs to be further clarified by subsequent experiments. In

addition, the gastric mucosa epithelium is covered by a thick mucous gel that allows secreted HCO3- to enter[18], The mucus-HCO_3^--barrier forms the gastrointestinal tract's first line of defense, preventing foreign substances from entering the cell cavity. GEORGE M. studied the effects of lithium intake on intestinal electrolyte and water transport in adult rats, and the results showed that chronic lithium intake has a unique mechanism of action[19].

Aldosterone appears to increase the permeability of the mucosal (intracluminal) barrier, allowing increased lithium to enter the colon epithelial cells[20]. Previous studies have shown that the therapeutic effect of Li^+ may be due to its inhibition of inositol 1-phosphatase, reducing the level of inositol and resulting in lower phosphatidyl inositol concentrations, especially in those neurons that are overstimulated. This alteration in phosphatidylinositol metabolism may help reset the sensitivity of those multifunctional receptors that produce second messengers, such as Ca^{2+}, cyclic GMP, and prostaglandins[21]. Berridge et al. found that lithium ions could directly inhibit the hydrolysis of inositol monophosphatase, resulting in the aggregation of inositol phosphate and the increase of cytoplasmic Ca^{2+} concentration. Using isolated sections of rat gastric fundus mucosa, C. CASCIANO et al. found that the hydrolysis of inositol phospholipid may be involved in the coupling stimulation of secretion leading to the secretion of $HCO3^-$. Subsequent experiments also confirmed that lithium ion can inhibit the hydrolysis of inositol monophosphatase, resulting in the aggregation of total inositol monophosphate, and then activate calmodulin-dependent phosphorylation of a series of cellular proteins, resulting in increased cytoplasmic calcium ion concentration and stimulating the secretion of $HCO3^-$ [22].

2.2 The regulatory effect of lithium ion on gastrointestinal epithelial transport

After oral administration of lithium preparations, human tissues absorb lithium mainly in a passive manner in the gastrointestinal tract[23]. There is a significant correlation between serum lithium and the potential difference of the rectal mucosa, and the potential difference across the rectal mucosa is increased in patients treated with lithium, which can be explained by the resistance of the rectal mucosa to vasopressin[24]. Most of the absorption of lithium in the colon of the rat occurs through the exchange of sodium, and the potential difference is reduced while sodium secretion is greatly increased. This is in contrast to the human colon, where potassium is exchanged with lithium ions and the potential difference increases[25]. It is known that when actively transported sugars or amino acids are added to the mucosal side, the transmural potential difference in the small intestine immediately increases. The potential increment caused by sugar (sugar evoked potential) has been shown to be closely related to the active transport of sugar itself. It was initially thought that this change in transmural potential difference was the result of increased activity of sodium ion pumps in mucosal cells[26].

Later, Hoshi and Komatsu hypothesized that this potential could be a diffusion potential associated with the movement of charged sodium glycocarrier complexes within the mucosal boundaries of epithelial cells, the driving force of which could be maintained by a non-electrogenerative sodium pump[27]. Both lithium and sodium are monovalent positive ions, and it has been previously reported that Li^+ will not be actively transported by the small intestine [33]. They found that Li^+ could only interact with the sugar carrier at the mucosal boundary, but could not replace Na^+ at the Na^+ pump site[28]. HAYASHI, H. et al studied the generation of incremental sugar-dependence of transwall potential (sugar-evoked potential) in Li^+ medium using the toad intestinal ectropion sac. When actively transported sugar was added to mucosal solution, a significant and immediate increase in potential difference (PD) was observed in Li^+- medium, although its maximum magnitude was smaller than that in Na+- medium. The salient features of evoked potentials

generated in Li^+ media are their relatively rapid spontaneous decay (failure of platform formation) and the independence of their oxygen-supplying structures. The results showed that Li^+ could interact with and stimulate glycocarriers at mucosal margins, but it would not be actively extruded from mucosal cells, and the generation of sugar-evoked potentials was related to the movement of glycocarrier complexes within the mucosal boundaries of epithelial cells[29].

2.3 Lithium ion and gastrointestinal smooth muscle

The fundus of the stomach is innervated by excitatory cholinergic and inhibitory non-adrenergic non-cholinergic (NANC) nerves[30]. Neurotransmission of NANC has been identified in many parts of the gastrointestinal tract and is associated with the release of nitric oxide (NO) under electrical stimulation[31]. In addition, NANC-mediated diastole has also been demonstrated to be mediated by NO formation in the gastric fundus of rats [32]. As a major NANC neurotransmitter, NO plays an important role in its physiology and function. NO is synthesized by nitric oxide synthase (NOS) and induces gastric fundus diastole in rats by stimulating the production of cGMP by guanosine cyclase. Experiments by Mehdi Ghasemi's team suggest that lithium may cause NANC-mediated damage to rat fundus diastole by interfering with the L-arginine /NO pathway in nitroergic nerves[33].

3. Lithium in gastrointestinal diseases

3.1 Lithium ions and salivary glands

Lithium, as a first-line treatment for bipolar disorder, is often accompanied by changes in saliva production during use, resulting in insufficient saliva production[34] .The role of lithium in digestive tract diseases in **Table.(2).** Salivary secretion is an important factor in maintaining oral health, and it performs mechanical cleaning and protection functions through various physiological and biochemical mechanisms. The regulatory role of lithium in gastrointestinal diseases in **Figure .(1)**.Therefore, the decline of salivary gland function can cause many adverse effects on an individual's oral health[35]. To this end, we understand the effects of a variety of psychoactive drugs on salivary gland function, such as tricyclic antidepressants, phenothiazine antipsychotics and lithium can inhibit salivary secretion and cause dry mouth syndrome. It is currently known that the anti-salivatory effects of tricyclic antidepressants and phenothiazine antipsychotics are mediated by blocking muscarinic receptors[36].

However, the anti-salivation mechanism of lithium is still unclear. It has been reported that lithium chloride can induce glycogen accumulation in the salivary glands of rats[35]. J Popovic et al. investigated the effect of acute and chronic lithium on salivation induced by agonists associated with receptor-associated membrane inositol phospholipid hydrolysis (carbaccholine and deoxyadrenaline) and adenylate cyclase activation (isoproterenol). The study found that chronic but non-acute lithium treatment significantly reduced carbachocholine and deoxyadrenaline induced salivary secretion, while isoproterenol induced salivary secretion did not change after acute or chronic lithium administration. Therefore, it can be concluded that insufficient salivary secretion during chronic lithium treatment may be caused by changes in the phosphatidylinositol cycle and inositol deficiency after agonist stimulation[37].

3.2 Chronic secretory diarrhea

With the constant change of people's dietary environment, diarrhea occurs more and more frequently, which has become an important medical and health problem[38]. Diarrhea is a common clinical symptom. It is usually accompanied by increased frequency of defecation, increased fecal water content[39], and

symptoms such as pus, blood and mucus. Clinical symptoms more than four weeks can be judged as chronic diarrhea[40]. Persistent and severe diarrhea can kill people, so effective control of diarrhea is essential. There are many causes of diarrhea, both drug and disease factors. There is relevant evidence that long-term abuse of laxatives can cause secretory diarrhea[39, 41, 42], Neoplasms secreting gastrointestinal peptides, villous adenomas and other neoplasms can also cause diarrhea. When the cause of diarrhea is unknown and the pathogenic factors cannot be effectively eliminated, drug intervention that changes the gastrointestinal electrolyte transport process can be used to stimulate intestinal absorption or inhibit intestinal secretion to treat the disease.

A clinical study found that patients with chronic secretory diarrhea treated with lithium carbonate had less clinical symptoms and no recurrence of diarrhea after stopping the drug[43]. However, researchers have not yet clarified the relationship between lithium carbonate and chronic secretory diarrhea. According to related reports, lithium carbonate is a drug that inhibits cyclic adenosine phosphate synthesis[44]. In human tissues, lithium carbonate may inhibit receptor-mediated cyclic adenosine phosphate synthesis by inhibiting adenylate cyclase[45]. The increase of cAMP in intestinal epithelial cells induces the increase of sodium-dependent chloride ion secretion, and at the same time blocks the absorption of sodium and chloride ions by the brush border, resulting in diarrhea[46, 47]. The inhibitory effect of lithium carbonate on cyclic adenosine phosphate may be the reason for its anti-secretion effect in the gut, so lithium carbonate may be effective against diarrhea mediated by cyclic adenosine phosphate pathway, but this effect needs further research to prove.

3.3 Irritable bowel syndrome (IBS)

Irritable bowel syndrome (IBS) is one of the common digestive diseases in clinic[48]. The main clinical manifestations are abdominal pain, frequency of defecation and changes in stool form[49]. There has been evidence that the pathogenesis of IBS is mainly the change of gastrointestinal motility and the increase of intestinal stimulation sensitivity. In addition, social environmental factors, dietary changes, and external influences can also induce IBS[50]. Visceral hypersensitivity is a common reaction in most patients with intestinal stress syndrome, and its discovery can provide a basis for the study of the physiology and pathology of IBS[51]. Lithium is a widely used drug for bipolar disorder that acts as a stomach protector. The effects of lithium on some tissues are mediated by nitric oxide (NO), which regulates gastrointestinal motility and mucosal integrity.

Hosein Shamshiri et al. found that chronic lithium administration attenuates visceral hypersensitivity, raises nociceptive thresholds, and reduces bowel frequency. L-NAME (a non-selective NO synthase (NOS) inhibitor) and aminoguanidine (a selective NOS inhibitor) reduced the notional receptive threshold and reduced the protective effect of lithium on visceral hypersensitivity. Further study found that L-NAME increased fecal frequency in both the lithium treatment group and the water treatment group, but the aminoguanidine did not increase. The pattern of defecation in lithium-treated rats shifted to hard faeces instead of soft and formless, but NOS inhibitors did not change the fecal consistency pattern. Based on the above conclusions, we know that chronic lithium has an analgesic effect on visceral hypersensitivity. Since NOS inhibitors weaken this effect, NO may play a protective role of lithium to a certain extent[52].

3.4 Hepatic ischemia/reperfusion Injury (I/RI)

IRI is a multifactorial process that affects liver function after major liver surgery, such as extended hepatectomy or liver transplantation performed by Pringle. Liver ischemia/reperfusion injury (IRI), which

damages liver cells and sinusoidal endothelial cells in the ischemic liver, may occur in clinical treatment of liver transplantation, liver tumor resection, trauma, circulatory shock, and other injuries. Paradoxically, the damage worsens as blood flow returns[53]. At present, the most studied aspects of IRI are the activation of phosphatidylinositol 3-kinase /Akt12 and extracellular signal-regulated kinase (ERK) cell survival pathway, inhibition of glycogen synthase kinase 3b (GSK3b) activity, reduction of apoptotic death and induction of autophagy[54]. Liver I/RI is the main cause of graft function loss after liver transplantation, which may seriously impair the function of the remaining liver after hepatectomy[55]. Lithium as an inhibitor of GSK-3β has beneficial effects on ischemia/reperfusion (I/RI) of the central nervous system, heart, and kidneys. Previous studies have shown that lithium chloride (LiCl) phosphorylates Ser9 residues and inhibits GSK-3β activity, thereby improving I/RI in other organs.

Nevertheless, the role of lithium in liver I/RI is unclear. In order to assess whether lithium has an effect on liver I/RI, Yongxiang Xia et al conducted a study using control mice and LiCl pre-treated groups, and found that the LiCl group significantly increased liver I/RI, as determined by serological and histological analysis. Acute and chronic LiCl treatment causes serious damage to liver I/RI, including apoptosis and increased oxidative stress. In order to further understand the mechanism of this damage, Yongxiang Xia et al. further studied and found that the activity of NF-kB was significantly down-regulated in LiCl pretreatment group. Moreover, the expression of NF-kB mediated protective genes such as anti-apoptotic genes (RAF2, cIAP2, Bfl-1 and cFLIP) and antioxidant genes MnSOD were significantly inhibited. These findings suggest that lithium aggravates hepatic ischemia/reperfusion injury by inhibiting GSK-3β/NF-kb mediated protective signaling pathways in mice[56].

Studies have also shown that acute lithium therapy does not prevent I/R damage. The experimental data indicate that the mechanisms mediated by GSK3b-, MAPK-, apoptosis - and autophagy are important pathways involved in the protective effects of chronic lithium therapy on liver I/R injury[54]. In addition, activation of the glycogen synthase kinase 3β (GSK3β) and extracellular signal-regulated kinase (ERK1/2) pathways during IRI are two major events that independently regulate autophagy. On the one hand, the GSK3β pathway indirectly regulates autophagy by down-regulating the activity of mTOR, which is known as a well-known autophagy inhibitor. Phosphorylation of ERK1/2, on the other hand, leads to activation of the beclin1 pathway, which is directly involved in the autophagy process. Based on these studies, Chunyi Kan et al., after inducing hepatic steatosis in rats, injected lithium chloride or normal saline for 3 days and performed hot ischemia for 60 minutes. After reperfusion, the rats were observed 30 min, 6, 24, 48 h. The results showed that liver injury was significantly reduced in the treatment group, and lithium chloride may protect hepatocytes from the effects of IRI by regulating autophagy induced by GSK3β and ERK1/2 pathways.

Therefore, lithium chloride may be a new strategy to protect fatty liver from the effects of hepatic IRI[57].

3.5 Colitis and colorectal cancer

Lithium has been used for more than decades as a neuroprotective drug in the treatment of bipolar disorder. It activates the Wnt/ beta-catenin signaling pathway in vivo and in vitro by directly and indirectly inhibiting GSK3b. The colon is one of the tissues susceptible to the Wnt signaling pathway, so it is necessary to explore the relationship between lithium and the colon[58].

Inflammatory bowel disease (IBD) is a multifactorial disease of unknown etiology characterized by oxidative stress, leukocyte infiltration, and elevated levels of inflammatory cytokines such as tumor necrosis

factor (TNF-a)[59]. It has been reported that lithium carbonate has a therapeutic effect on ulcerative colitis[60]. The use of lithium chloride (GSK-3β inhibitor) induces MYC transcription, expression of MYC protein and Wnt/MYC target gene subset in colon epithelial cells, promoting recovery from acute DSS induced injury. The use of 10058-F4 can inhibit MYC function and lead to reduced lithium action[61]. Ali Daneshmand et al. found in a 2,4,6-trinitrobenzene sulfonic acid (TNBS) -induced IBD model that lithium chloride significantly improved the macroscopic and histological features of colon injury. MPO activity, MDA levels, and TNF-a levels were also reduced. And in experiments with glibenclamide, a potassium channel blocker, it was found that glibenclamide reversed the effect of lithium on the marker. Studies have shown that the regulatory mechanism of potassium channels plays an important role in the inflammatory process, especially the activation of ATP-sensitive potassium channels can inhibit the production of mitochondrial reactive oxygen species (ROS) and reduce the production of inflammatory factors, thus playing an anti-inflammatory role[62].

Other studies have also found that large doses of lithium chloride have toxic effects on the intestine, and 200 mg/kg LiCl may induce colon inflammation in mice by activating F4/80 positive macrophages, inhibiting the expression of IgA coding genes in plasma cells and Pigr and Claudin-15 expressions in colon epithelial cells[58]. In addition, recent evidence suggests that dysregulation of the gut microbiota and its metabolites are important triggers of IBD inflammation and not just the result of chronic inflammation[63]. The gut microbiota has an impact on the persistence of IBD, and the fecal microbiota composition of patients with IBD differs from that of healthy individuals[64] . This difference is manifested by significant downregulation of diversity, reduction of probiotics and changes in biota metabolites, which are related to the progression and outcome of IBD[65]. There is evidence that lithium carbonate can alleviate IBD symptoms by regulating gut microbiota and metabolism[66, 67] . Experimental data from Shengjie Huang et al suggest that lithium carbonate improves DSS-induced colitis in a GPR43-dependent manner. The underlying mechanisms are related to regulation of gut microbiota structure and composition, increased metabolite SCFA production, and activation of anti-inflammatory Treg cell responses in a GPR43-dependent manner, which may provide a new direction for the treatment of patients with IBD. In conclusion, the use of lithium salt in the treatment of inflammatory bowel disease may have important clinical significance[68].

Colorectal cancer (CRC) is the third most prevalent cancer type in the world. Patients with colorectal cancer and metastatic colorectal cancer have 5-year survival rates of less than 60% and 20%, respectively. At present, the main treatment for CRC is surgery, which is often combined with chemotherapy and radiation therapy. Because tumors are resistant to chemotherapy and radiation. In recent years, molecularly targeted drugs have been proposed for the treatment of colorectal cancer. The transcription factor NF-κB has been shown to be critical for tumor progression and chemotherapy resistance in colorectal cancer by increasing the expression of some target genes[69].

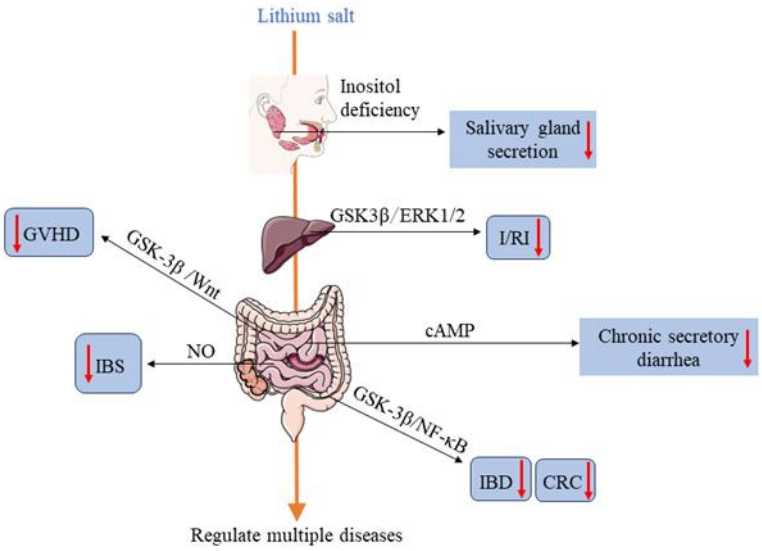
Simultaneously, previous studies have shown that GSK-3β can regulate NF-κB activity[70-73]. Glycogen synthase kinase 3β(GSK-3β) is a serine/threonine protein kinase that has been identified as a potential therapeutic target for a variety of human cancers. In addition, oxidative stress is strongly associated with all aspects of cancer. There is evidence that lithium is a specific and non-competitive inhibitor of GSK-3β in vitro and in vivo. Huili Li et al. demonstrated in human colon cancer cell line SW480 that lithium chloride increases reactive oxygen species (ROS) production and leads to decreased cell survival and proliferation via the ROS/GSK-3β/NF-κB pathway. The results suggest that GSK-3β may be a new potential therapeutic target for colorectal cancer, and lithium may become a new potential anti-tumor drug[69].

3.6 graft-versus-host disease (GVHD)

Severe intestinal GVHD following allogeneic hematologic cell transplantation (HCT) leads to mucosal ulceration and induces innate and adaptive immune responses that amplify and perpetuate GVHD and associated barrier dysfunction. Intestinal involvement is a major source of morbidity and mortality in acute GVHD targets[74]. The histological features of intestinal GVHD are apoptosis of epithelial cells at the base of the crypt and secondary loss of cells and crypts[75, 76]. In extremely severe cases, GVHD can lead to progressive recessus loss and mucosal exfoliation of large segments of the intestine[77-79]. There is evidence that Wnt signaling, including downstream β-catenin/ TCF4-mediated transcription, is critical for epithelial stem cell replication, cryptogenesis, and crypto proliferation[80, 81]. Lithium carbonate, as an inhibitor of glycogen synthase kinase 3β (GSK-3β)[82], can promote β-catenin/ TCF4-mediated transcription[83], that is, induce Wnt signaling, enhance intestinal crypt proliferation and mucosal repair[74]. Inhibition of Wnt, β-catenin or Tcf4 in animal models revealed intestinal recess loss and mucosal exfoliation[81, 84-86].

Conversely, induction of Wnt signaling in vitro and in animal models leads to epithelial cell proliferation[87, 88] . HansClevers' research group also found that by inducing Wnt signaling in isolated intestinal stem cells, self-renewing intestinal recess organoids could be generated in vitro[89]. Induction of Wnt signal transduction by recombinant Wnt agonist R-spondin1 has also been shown to repair radiation-induced intestinal mucosal injury, thereby inhibiting systemic GVHD in HCT rat models[90]. These experimental data suggest that lithium can potentially stimulate intestinal mucosal recovery and resolve mucosal inflammation in patients with severe intestinal GVHD and extensive intestinal mucosal dissection.

Figure 1: The regulatory role of lithium in gastrointestinal diseases



A brief description of The regulatory role of lithium in gastrointestinal diseases：1）During lithium treatment, which change in the phosphatidylinositol cycle and inositol deficiency can cause insufficient salivary secretion；2）Lithium salts treat secretory diarrhea by inhibiting the synthesis of cyclic adenosine monophosphate；3）Lithium salts treat IBS by reducing visceral hypersensitivity and reducing bowel frequency，NO play a protective role of lithium；4）lithium chloride may protect hepatocytes from the effects of IRI by regulating autophagy induced by GSK3 β and ERK1/2

pathways； 5） lithium carbonate alleviate IBD symptoms by regulating gut microbiota and metabolism； lithium increases reactive oxygen species (ROS) production and leads to decreased cell survival and proliferation via the ROS/GSK-3 β /NF- κ B pathway,lithium may become a new potential anti-tumor drug； 6） Lithium induce Wnt signaling,enhance intestinal crypt proliferation and mucosal repair,to treat GVHD and extensive intestinal mucosal dissection.

Table 1 The abbreviations of the review

abbreviations	full names
Li	Lithium
PD	potential difference
NANC	non-adrenergic non-cholinergic
NO	nitric oxide
NOS	nitric oxide synthase
IBS	irritable bowel syndrome
L-NAME	non-selective NO synthase (NOS) inhibitor
I/RI	ischemia/reperfusion injury
ERK	extracellular signal-regulated kinase
GSK3b	glycogen synthase kinase 3b
TNF-a	tumor necrosis factor- a
TNBS	trinitrobenzene sulfonic acid
CRC	Colorectal cancer
ROS	reactive oxygen species
GVHD	acute graft-versus-host disease
HCT	hematologic cell transplantation

Table 2 The role of lithium in digestive tract diseases

Disease	Mechanism	Reference
Insufficient saliva production	Inositol deficiency	[39]
Chronic secretory diarrhea	Inhibit cAMP	[51,52]
IBS	NO pathway	[57]
I/RI	Inhibit the expression of GSK-3b/NF-kB-mediated protective genes； Regulate the GSK-3β and ERK1/2 pathways	[59]、[61,62]
IBD	Inhibit GSK-3β, induce the expression of Myc; ATP-sensitive potassium channel activation; Regulate gut microbiota and metabolism	[67]、[69,71,72]

CRC	ROS/GSK-3β/NF-κB	[74]
GVHD	Inhibit GSK-3β, enhance intestinal crypt proliferation and mucosal repair	[79]

4. Conclusion

Lithium is commonly used as a drug for bipolar disorder. It has many physiological functions, and its application effect and mechanism in the field of gastrointestinal tract are gradually known. Because it has the effect of relieving abdominal pain, diarrhea and anti-colon cancer, more and more studies have applied it to digestive tract diseases, which provides a new idea for the treatment of gastrointestinal diseases.

Supplementary Materials: Not applicable, all information in this review can be found in the reference list.

Author Contributions: G.Y.G and M.W wrote the manuscript. H.Y.Z, R.C, C.Y.L, F. W, T.Z, Y.D, X. Y. M, X. edh, and Q.D collect the literature. J.Y.X primarily revised and finalized manuscript R.X. revised the manuscript for clarity and style. All authors read and approved the final manuscript.

Funding: This study was supported by research grants the National Natural Science Foundation of China (No.81660099; No. 82170628; No.81970541; No.31960151; No.32160208; No.81770610). This study was supported by Guizhou Science and Technology Department (Qiankehe platform talents (2021-5647)); This study was supported by Zunyi Science and Technology Bureau (Outstanding Young Talents in Zunyi City(2018-9;2020-1)); This study was supported by Collaborative Innovation Center of Chinese Ministry of Education (2020-39 ）; This study was supported by Guizhou Science and Technology Department (Qiankehe foundation-ZK (2021–major project 004); the Science and Technology Plan Project of Guizhou Province (QIAN KE HE JI CHU-ZK(2023)YI BAN556).

Institutional Review Board Statement: No ethics approval was required for this review that did not involve patients or patient data.

Informed Consent Statement: We have obtained consents to publish this paper from all the participants of this study.

Data Availability Statement: Not applicable, all information in this review can be found in the reference list.

Acknowledgments: We also thank Professor Biguang Tuo (Department of Gastroenterology, Affiliated Hospital to Zunyi Medical University) for highly professional services.

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

References

1 Schou M. BIOLOGY AND PHARMACOLOGY OF THE LITHIUM ION. *Pharmacological Reviews* 1957; **9**(1): 17-58

2 Stein RS, Beaman C, Ali MY, Hansen R, Jenkins DD, Jume'an HG. Lithium carbonate attenuation of chemotherapy-induced neutropenia. *N Engl J Med* 1977; **297**(8): 430-431 [PMID: 882113 DOI: 10.1056/NEJM197708252970807]

3 Chiu CT, Chuang DM. Neuroprotective action of lithium in disorders of the central nervous system. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2011; **36**(6): 461-476 [PMID: 21743136 PMCID: PMC3172812 DOI: 10.3969/j.issn.1672-7347.2011.06.001]

4 Chen PH, Chao TF, Kao YH, Chen YJ. Lithium interacts with cardiac remodeling: the fundamental value in the pharmacotherapy of bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **88**: 208-214 [PMID: 30053574 DOI: 10.1016/j.pnpbp.2018.07.018]

5 Rybakowski JK. Antiviral, immunomodulatory, and neuroprotective effect of lithium. *J Integr Neurosci* 2022; **21**(2): 68 [PMID: 35364656 DOI: 10.31083/j.jin2102068]

6 Tondo L, Alda M, Bauer M, Bergink V, Grof P, Hajek T, Lewitka U, Licht RW, Manchia M, Muller-Oerlinghausen B, Nielsen RE, Selo M, Simhandl C, Baldessarini RJ, International Group for Studies of L. Clinical use of lithium salts: guide for users and prescribers. *Int J Bipolar Disord* 2019; **7**(1): 16 [PMID: 31328245 PMCID: PMC6643006 DOI: 10.1186/s40345-019-0151-2]

7 Kamal ZM, Dutta S, Rahman S, Etando A, Hasan E, Nahar SN, Wan Ahmad Fakuradzi WFS, Sinha S, Haque M, Ahmad R. Therapeutic Application of Lithium in Bipolar Disorders: A Brief Review. *Cureus* 2022; **14**(9): e29332 [PMID: 36159362 PMCID: PMC9484534 DOI: 10.7759/cureus.29332]

8 Ostrovskaya RU, Ivanov SV, Durnev AD. Neuroprotective Lithium Salts Protect Pancreatic beta-capital ES, Cyrillicells from Damage. *Bull Exp Biol Med* 2018; **165**(6): 758-762 [PMID: 30353339 DOI: 10.1007/s10517-018-4259-7]

9 Medic B, Stojanovic M, Stimec BV, Divac N, Vujovic KS, Stojanovic R, Colovic M, Krstic D, Prostran M. Lithium - Pharmacological and Toxicological Aspects: The Current State of the Art. *Curr Med Chem* 2020; **27**(3): 337-351 [PMID: 30182841 DOI: 10.2174/0929867325666180904124733]

10 Seidler U, Song P, Xiao F, Riederer B, Bachmann O, Chen M. Recent advances in the molecular and functional characterization of acid/base and electrolyte transporters in the basolateral membranes of gastric and duodenal epithelial cells. *Acta Physiol (Oxf)* 2011; **201**(1): 3-20 [PMID: 20331540 DOI: 10.1111/j.1748-1716.2010.02107.x]

11 Negussie AB, Dell AC, Davis BA, Geibel JP. Colonic Fluid and Electrolyte Transport 2022: An Update. *Cells* 2022; **11**(10) [PMID: 35626748 PMCID: PMC9139964 DOI: 10.3390/cells11101712]

12 Keely SJ, Barrett KE. Intestinal secretory mechanisms and diarrhea. *Am J Physiol Gastrointest Liver Physiol* 2022; **322**(4): G405-G420 [PMID: 35170355 PMCID: PMC8917926 DOI: 10.1152/ajpgi.00316.2021]

13 Murek M, Kopic S, Geibel J. Evidence for intestinal chloride secretion. *Exp Physiol* 2010; **95**(4): 471-478 [PMID: 20233891 DOI: 10.1113/expphysiol.2009.049445]

14 He J, Yang X, Guo Y, Zhang F, Wan H, Sun X, Tuo B, Dong H. Ca(2+) signaling in HCO(3)(-) secretion and protection of upper GI tract. *Oncotarget* 2017; **8**(60): 102681-102689 [PMID: 29254280 PMCID: PMC5731990 DOI: 10.18632/oncotarget.21840]

15 Zhang F, Wan H, Yang X, He J, Lu C, Yang S, Tuo B, Dong H. Molecular mechanisms of caffeine-mediated intestinal epithelial ion transports. *Br J Pharmacol* 2019; **176**(11): 1700-1716 [PMID: 30808064 PMCID: PMC6514291 DOI: 10.1111/bph.14640]

16 Takeuchi K, Amagase K. Roles of Cyclooxygenase, Prostaglandin E2 and EP Receptors in Mucosal Protection and Ulcer Healing in the Gastrointestinal Tract. *Curr Pharm Des* 2018; **24**(18): 2002-2011 [PMID: 29956615 DOI: 10.2174/1381612824666180629111227]

17 Wong RK, Boedeker B, Hickey TM, Wilkinson DS, Johnson LF. Lithium chloride: protective and antisecretory properties in rats. *Gastroenterology* 1984; **87**(2): 362-371 [PMID: 6329891]

18 Rees WD, Turnberg LA. Mechanisms of gastric mucosal protection: a role for the 'mucus-bicarbonate' barrier. *Clin Sci (Lond)* 1982; **62**(4): 343-348 [PMID: 6175466 DOI: 10.1042/cs0620343]

19 Feldman GM, Mann JJ, Charney AN. Effect of lithium ingestion on water and electrolyte transport in rat intestine. *Gastroenterology* 1981; **81**(5): 892-897 [PMID: 6269945]

20 Dolman D, Edmonds CJ, Salas-Coll C. Effect of aldosterone on lithium permeability of rat colon mucosa. *J Endocrinol* 1976; **70**(1): 135-140 [PMID: 932598 DOI: 10.1677/joe.0.0700135]

21 Berridge MJ, Downes CP, Hanley MR. Lithium amplifies agonist-dependent phosphatidylinositol responses in brain and salivary glands. *Biochem J* 1982; **206**(3): 587-595 [PMID: 7150264 PMCID: PMC1158627 DOI: 10.1042/bj2060587]

22 Casciano C, Bennun A. Effect of Li+ on the secretion of HCO3- in rat fundic tissue. *Biochem Soc Trans* 1989; **17**(6): 1111-1112 [PMID: 2560741 DOI: 10.1042/bst0171111]

23 Phillips JD, Davie RJ, Birch NJ. Tissue uptake of lithium in guinea-pig isolated intestinal mucosa after chronic lithium ingestion. *Biochem Soc Trans* 1990; **18**(4): 653-654 [PMID: 2276495 DOI: 10.1042/bst0180653]

24 Rask-Madsen J, Baastrup PC, Schwartz M. Lithium-induced hyperpolarization of the human rectum in vivo. *Br Med J* 1972; **2**(5812): 496-498 [PMID: 5031209 PMCID: PMC1788317 DOI: 10.1136/bmj.2.5812.496]

25 Dolman DE, Edmonds CJ. The effect of lithium on the transport of sodium, potassium and chloride by the colon of normal and sodium-depleted rats. *J Physiol* 1976; **259**(3): 771-783 [PMID: 957263 PMCID: PMC1309063 DOI: 10.1113/jphysiol.1976.sp011494]

26 Kohn PG, Smyth DH, Wright EM. Effects of amino acids, dipeptides and disaccharides on the electric potential across rat small intestine. *J Physiol* 1968; **196**(3): 723-746 [PMID: 5664239 PMCID: PMC1351774 DOI: 10.1113/jphysiol.1968.sp008533]

27 Hoshi T, Komatsu Y. Effects of anoxia and metabolic inhibitors on the sugar-evoked potential and demonstration of sugar-outflow potential in toad intestine. *Tohoku J Exp Med* 1970; **100**(1): 47-59 [PMID: 5416555 DOI: 10.1620/tjem.100.47]

28 Bihler I, Adamic S. The effect of lithium on intestinal sugar transport. *Biochim Biophys Acta* 1967; **135**(3): 466-474 [PMID: 6048817 DOI: 10.1016/0005-2736(67)90036-3]

29 Hayashi H, Saito Y, Hoshi T. Sugar-dependent increment of the transmural potential of isolated small intestine in Li plus-medium. *Tohoku J Exp Med* 1971; **103**(2): 119-128 [PMID: 5580591 DOI: 10.1620/tjem.103.119]

30 Li CG, Rand MJ. Nitric oxide and vasoactive intestinal polypeptide mediate non-adrenergic, non-cholinergic inhibitory transmission to smooth muscle of the rat gastric fundus. *Eur J Pharmacol* 1990; **191**(3): 303-309 [PMID: 1964906 DOI: 10.1016/0014-2999(90)94162-q]

31 Desai KM, Sessa WC, Vane JR. Involvement of nitric oxide in the reflex relaxation of the stomach to accommodate food or fluid. *Nature* 1991; **351**(6326): 477-479 [PMID: 1675430 DOI: 10.1038/351477a0]

32 Zhang L, Lu W, Lu C, Guo Y, Chen X, Chen J, Xu F, Wan H, Dong H. Beneficial effect of capsaicin via TRPV4/EDH signals on mesenteric arterioles of normal and colitis mice. *J Adv Res* 2022; **39**: 291-303 [PMID: 35777913 PMCID: PMC9263647 DOI: 10.1016/j.jare.2021.11.001]

33 Ghasemi M, Karimollah AR, Dehpour AR. Nitric oxide involvement in the effect of acute lithium administration on the nonadrenergic noncholinergic-mediated relaxation of rat gastric fundus. *Nitric Oxide* 2007; **17**(3-4): 152-159 [PMID: 17889573 DOI: 10.1016/j.niox.2007.08.002]

34 Markitziu A, Shani J, Avni J. Salivary gland function in patients on chronic lithium treatment. *Oral Surg Oral Med Oral Pathol* 1988; **66**(5): 551-557 [PMID: 3200558 DOI: 10.1016/0030-4220(88)90374-x]

35 Souza DN, Mendes FM, Nogueira FN, Simoes A, Nicolau J. Lithium Induces Glycogen Accumulation in Salivary Glands of the Rat. *Biol Trace Elem Res* 2016; **169**(2): 271-278 [PMID: 26155966 DOI: 10.1007/s12011-015-0434-0]

36 Mornstad H, von Knorring L, Forsgren L, Holmgren S. Long-term effects of two principally different antidepressant drugs on saliva secretion and composition. *Scand J Dent Res* 1986; **94**(5): 461-470 [PMID: 2948270 DOI: 10.1111/j.1600-0722.1986.tb01788.x]

37 Popovic J, Krsljak E, Grbovic L, Stojic D. The effects of acute and chronic lithium treatment on rat submandibular salivation. *Oral Dis* 2005; **11**(2): 100-103 [PMID: 15752083 DOI: 10.1111/j.1601-0825.2004.01066.x]

38 Li Y, Xia S, Jiang X, Feng C, Gong S, Ma J, Fang Z, Yin J, Yin Y. Gut Microbiota and Diarrhea: An Updated Review. *Front Cell Infect Microbiol* 2021; **11**: 625210 [PMID: 33937093 PMCID: PMC8082445 DOI: 10.3389/fcimb.2021.625210]

39 Sokic-Milutinovic A, Pavlovic-Markovic A, Tomasevic RS, Lukic S. Diarrhea as a Clinical Challenge: General Practitioner Approach. *Dig Dis* 2022; **40**(3): 282-289 [PMID: 33971655 DOI: 10.1159/000517111]

40 Gomez-Escudero O, Remes-Troche JM. Approach to the adult patient with chronic diarrhea: A literature review. *Rev Gastroenterol Mex (Engl Ed)* 2021; **86**(4): 387-402 [PMID: 34389290 DOI: 10.1016/j.rgmxen.2021.08.007]

41 DuPont HL. Persistent Diarrhea: A Clinical Review. *JAMA* 2016; **315**(24): 2712-2723 [PMID: 27357241 DOI: 10.1001/jama.2016.7833]

42 Moon C, Zhang W, Sundaram N, Yarlagadda S, Reddy VS, Arora K, Helmrath MA, Naren AP. Drug-induced secretory diarrhea: A role for CFTR. *Pharmacol Res* 2015; **102**: 107-112 [PMID: 26429773 PMCID: PMC4684461 DOI: 10.1016/j.phrs.2015.08.024]

43 Owyang C. Treatment of chronic secretory diarrhea of unknown origin by lithium carbonate. *Gastroenterology* 1984; **87**(3): 714-718 [DOI: 10.1016/0016-5085(84)90548-1]

44 Rosenbaum A, Maruta T, Richelson E. Series on pharmacology in practice. 1. Drugs that alter mood. II. Lithium. Proceedings of the Mayo Clinic Proceedings; 1979. 401-407

45 Czarnywojtek A, Zgorzalewicz-Stachowiak M, Czarnocka B, Sawicka-Gutaj N, Gut P, Krela-Kazmierczak I, Ruchala M. Effect of lithium carbonate on the function of the thyroid gland: mechanism of action and clinical implications. *J Physiol Pharmacol* 2020; **71**(2) [PMID: 32633237 DOI: 10.26402/jpp.2020.2.03]

46 Fenton RA, Murali SK, Kaji I, Akiba Y, Kaunitz JD, Kristensen TB, Poulsen SB, Dominguez Rieg JA, Rieg T. Adenylyl Cyclase 6 Expression Is Essential for Cholera Toxin-Induced Diarrhea. *J Infect Dis* 2019; **220**(11): 1719-1728 [PMID: 30624615 PMCID: PMC6941499 DOI: 10.1093/infdis/jiz013]

47 Pongkorpsakol P, Pathomthongtaweechai N, Srimanote P, Soodvilai S, Chatsudthipong V, Muanprasat C. Inhibition of cAMP-activated intestinal chloride secretion by diclofenac: cellular mechanism and potential application in cholera. *PLoS Negl Trop Dis* 2014; **8**(9): e3119 [PMID: 25188334 PMCID: PMC4154654 DOI: 10.1371/journal.pntd.0003119]

48 Mansueto P, D'Alcamo A, Seidita A, Carroccio A. Food allergy in irritable bowel syndrome: The case of non-celiac wheat sensitivity. *World J Gastroenterol* 2015; **21**(23): 7089-7109 [PMID: 26109796 PMCID: PMC4476871 DOI: 10.3748/wjg.v21.i23.7089]

49 La JH, Kim TW, Sung TS, Kim HJ, Kim JY, Yang IS. Increase in neurokinin-1 receptor-mediated colonic motor response in a rat model of irritable bowel syndrome. *World J Gastroenterol* 2005; **11**(2): 237-241 [PMID: 15633223 PMCID: PMC4205409 DOI: 10.3748/wjg.v11.i2.237]

50 Camilleri M, Heading RC, Thompson WG. Clinical perspectives, mechanisms, diagnosis and management of irritable bowel syndrome. *Aliment Pharmacol Ther* 2002; **16**(8): 1407-1430 [PMID: 12182741 DOI: 10.1046/j.1365-2036.2002.01305.x]

51 Paine P. Review article: current and future treatment approaches for pain in IBS. *Aliment Pharmacol Ther* 2021; **54 Suppl 1**: S75-S88 [PMID: 34927753 DOI: 10.1111/apt.16550]

52 Shamshiri H, Paragomi P, Paydar MJ, Moezi L, Bahadori M, Behfar B, Ardalan FA, Dehpour AR. Antinociceptive effect of chronic lithium on visceral hypersensitivity in a rat model of diarrhea-predominant irritable bowel syndrome: The role of nitric oxide pathway. *J Gastroenterol Hepatol* 2009; **24**(4): 672-680 [PMID: 19032458 DOI: 10.1111/j.1440-1746.2008.05652.x]

53 Jaeschke H. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. *Am J Physiol Gastrointest Liver Physiol* 2003; **284**(1): G15-26 [PMID: 12488232 DOI: 10.1152/ajpgi.00342.2002]

54 Liu A, Fang H, Dahmen U, Dirsch O. Chronic lithium treatment protects against liver ischemia/reperfusion injury in rats. *Liver Transpl* 2013; **19**(7): 762-772 [PMID: 23696274 DOI: 10.1002/lt.23666]

55 Burroughs AK, Sabin CA, Rolles K, Delvart V, Karam V, Buckels J, O'Grady JG, Castaing D, Klempnauer J, Jamieson N, Neuhaus P, Lerut J, de Ville de Goyet J, Pollard S, Salizzoni M, Rogiers X, Muhlbacher F, Garcia Valdecasas JC, Broelsch C, Jaeck D, Berenguer J, Gonzalez EM, Adam R, European Liver Transplant A. 3-month and 12-month mortality after first liver transplant in

481 adults in Europe: predictive models for outcome. *Lancet* 2006; **367**(9506): 225-232 [PMID: 16427491 DOI:
482 10.1016/S0140-6736(06)68033-1]
483 56 Xia Y, Rao J, Yao A, Zhang F, Li G, Wang X, Lu L. Lithium exacerbates hepatic ischemia/reperfusion injury by inhibiting
484 GSK-3beta/NF-kappaB-mediated protective signaling in mice. *Eur J Pharmacol* 2012; **697**(1-3): 117-125 [PMID: 23051669 DOI:
485 10.1016/j.ejphar.2012.09.009]
486 57 Kan C, Liu A, Fang H, Dirsch O, Dahmen U, Boettcher M. Induction of autophagy reduces ischemia/reperfusion injury in
487 steatotic rat livers. *J Surg Res* 2017; **216**: 207-218 [PMID: 28807209 DOI: 10.1016/j.jss.2017.04.012]
488 58 Lei Z, Yang L, Lei Y, Yang Y, Zhang X, Song Q, Chen G, Liu W, Wu H, Guo J. High dose lithium chloride causes colitis
489 through activating F4/80 positive macrophages and inhibiting expression of Pigr and Claudin-15 in the colon of mice. *Toxicology*
490 2021; **457**: 152799 [PMID: 33901603 DOI: 10.1016/j.tox.2021.152799]
491 59 Daneshmand A, Rahimian R, Mohammadi H, Ejtemaee-Mehr S, Tavangar SM, Babaei Kelishomi R, Dehpour AR. Protective
492 effects of lithium on acetic acid-induced colitis in rats. *Dig Dis Sci* 2009; **54**(9): 1901-1907 [PMID: 19082724 DOI:
493 10.1007/s10620-008-0569-3]
494 60 Zisook S. Ulcerative colitis: case responding to treatment with lithium carbonate. *JAMA* 1972; **219**(6): 755 [PMID: 5066706]
495 61 Raup-Konsavage WM, Cooper TK, Yochum GS. A Role for MYC in Lithium-Stimulated Repair of the Colonic Epithelium
496 After DSS-Induced Damage in Mice. *Dig Dis Sci* 2016; **61**(2): 410-422 [PMID: 26320084 DOI: 10.1007/s10620-015-3852-0]
497 62 Daneshmand A, Mohammadi H, Rahimian R, Habibollahi P, Fakhfouri G, Talab SS, Mehr SE, Dehpour AR. Chronic lithium
498 administration ameliorates 2,4,6-trinitrobenzene sulfonic acid-induced colitis in rats; potential role for adenosine triphosphate
499 sensitive potassium channels. *J Gastroenterol Hepatol* 2011; **26**(7): 1174-1181 [PMID: 21401719 DOI:
500 10.1111/j.1440-1746.2011.06719.x]
501 63 Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nat Rev Gastroenterol*
502 *Hepatol* 2020; **17**(4): 223-237 [PMID: 32076145 DOI: 10.1038/s41575-019-0258-z]
503 64 Halfvarson J, Brislawn CJ, Lamendella R, Vazquez-Baeza Y, Walters WA, Bramer LM, D'Amato M, Bonfiglio F, McDonald D,
504 Gonzalez A, McClure EE, Dunklebarger MF, Knight R, Jansson JK. Dynamics of the human gut microbiome in inflammatory bowel
505 disease. *Nat Microbiol* 2017; **2**: 17004 [PMID: 28191884 PMCID: PMC5319707 DOI: 10.1038/nmicrobiol.2017.4]
506 65 Machiels K, Joossens M, Sabino J, De Preter V, Arijs I, Eeckhaut V, Ballet V, Claes K, Van Immerseel F, Verbeke K, Ferrante M,
507 Verhaegen J, Rutgeerts P, Vermeire S. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium
508 prausnitzii defines dysbiosis in patients with ulcerative colitis. *Gut* 2014; **63**(8): 1275-1283 [PMID: 24021287 DOI:
509 10.1136/gutjnl-2013-304833]
510 66 Song L, Qu D, Ouyang P, Ding X, Wu P, Guan Q, Yang L. The regulatory effects of phytosterol esters (PSEs) on gut flora and
511 faecal metabolites in rats with NAFLD. *Food & function* 2020; **11**(1): 977-991
512 67 Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nature reviews*
513 *Gastroenterology & hepatology* 2020; **17**(4): 223-237
514 68 Huang S, Hu S, Liu S, Tang B, Liu Y, Tang L, Lei Y, Zhong L, Yang S, He S. Lithium carbonate alleviates colon inflammation
515 through modulating gut microbiota and Treg cells in a GPR43-dependent manner. *Pharmacol Res* 2022; **175**: 105992 [PMID: 34801681
516 DOI: 10.1016/j.phrs.2021.105992]
517 69 Li H, Huang K, Liu X, Liu J, Lu X, Tao K, Wang G, Wang J. Lithium chloride suppresses colorectal cancer cell survival and
518 proliferation through ROS/GSK-3beta/NF-kappaB signaling pathway. *Oxid Med Cell Longev* 2014; **2014**: 241864 [PMID: 25002914
519 PMCID: PMC4070474 DOI: 10.1155/2014/241864]
520 70 Coghlan MP, Culbert AA, Cross DA, Corcoran SL, Yates JW, Pearce NJ, Rausch OL, Murphy GJ, Carter PS, Roxbee Cox L,
521 Mills D, Brown MJ, Haigh D, Ward RW, Smith DG, Murray KJ, Reith AD, Holder JC. Selective small molecule inhibitors of glycogen

synthase kinase-3 modulate glycogen metabolism and gene transcription. *Chem Biol* 2000; **7**(10): 793-803 [PMID: 11033082 DOI: 10.1016/s1074-5521(00)00025-9]

71 Hoeflich KP, Luo J, Rubie EA, Tsao M-S, Jin O, Woodgett JR. Requirement for glycogen synthase kinase-3β in cell survival and NF-κB activation. *Nature* 2000; **406**(6791): 86-90

72 Ougolkov AV, Bone ND, Fernandez-Zapico ME, Kay NE, Billadeau DD. Inhibition of glycogen synthase kinase-3 activity leads to epigenetic silencing of nuclear factor κB target genes and induction of apoptosis in chronic lymphocytic leukemia B cells. *Blood, The Journal of the American Society of Hematology* 2007; **110**(2): 735-742

73 Ougolkov AV, Fernandez-Zapico ME, Savoy DN, Urrutia RA, Billadeau DD. Glycogen synthase kinase-3β participates in nuclear factor κB–mediated gene transcription and cell survival in pancreatic cancer cells. *Cancer research* 2005; **65**(6): 2076-2081

74 Steinbach G, Hockenbery DM, Huls G, Furlong T, Myerson D, Loeb KR, Fann JR, Castilla-Llorente C, McDonald GB, Martin PJ. Pilot study of lithium to restore intestinal barrier function in severe graft-versus-host disease. *PLoS One* 2017; **12**(8): e0183284 [PMID: 28817727 PMCID: PMC5560707 DOI: 10.1371/journal.pone.0183284]

75 Sale GE, Shulman HM, McDonald GB, Thomas ED. Gastrointestinal graft-versus-host disease in man. A clinicopathologic study of the rectal biopsy. *Am J Surg Pathol* 1979; **3**(4): 291-299 [PMID: 44107 DOI: 10.1097/00000478-197908000-00001]

76 Ponec RJ, Hackman RC, McDonald GB. Endoscopic and histologic diagnosis of intestinal graft-versus-host disease after marrow transplantation. *Gastrointest Endosc* 1999; **49**(5): 612-621 [PMID: 10228260 DOI: 10.1016/s0016-5107(99)70390-1]

77 Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, Lerner KG, Thomas ED. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation* 1974; **18**(4): 295-304 [PMID: 4153799 DOI: 10.1097/00007890-197410000-00001]

78 Spencer GD, Shulman HM, Myerson D, Thomas ED, McDonald GB. Diffuse intestinal ulceration after marrow transplantation: a clinicopathologic study of 13 patients. *Hum Pathol* 1986; **17**(6): 621-633 [PMID: 3011641 DOI: 10.1016/s0046-8177(86)80135-6]

79 Melson J, Jakate S, Fung H, Arai S, Keshavarzian A. Crypt loss is a marker of clinical severity of acute gastrointestinal graft-versus-host disease. *Am J Hematol* 2007; **82**(10): 881-886 [PMID: 17570511 DOI: 10.1002/ajh.20976]

80 Clevers H. The intestinal crypt, a prototype stem cell compartment. *Cell* 2013; **154**(2): 274-284 [PMID: 23870119 DOI: 10.1016/j.cell.2013.07.004]

81 Pinto D, Gregorieff A, Begthel H, Clevers H. Canonical Wnt signals are essential for homeostasis of the intestinal epithelium. *Genes Dev* 2003; **17**(14): 1709-1713 [PMID: 12865297 PMCID: PMC196179 DOI: 10.1101/gad.267103]

82 Klein PS, Melton DA. A molecular mechanism for the effect of lithium on development. *Proc Natl Acad Sci U S A* 1996; **93**(16): 8455-8459 [PMID: 8710892 PMCID: PMC38692 DOI: 10.1073/pnas.93.16.8455]

83 Hedgepeth CM, Conrad LJ, Zhang J, Huang HC, Lee VM, Klein PS. Activation of the Wnt signaling pathway: a molecular mechanism for lithium action. *Dev Biol* 1997; **185**(1): 82-91 [PMID: 9169052 DOI: 10.1006/dbio.1997.8552]

84 Kuhnert F, Davis CR, Wang HT, Chu P, Lee M, Yuan J, Nusse R, Kuo CJ. Essential requirement for Wnt signaling in proliferation of adult small intestine and colon revealed by adenoviral expression of Dickkopf-1. *Proc Natl Acad Sci U S A* 2004; **101**(1): 266-271 [PMID: 14695885 PMCID: PMC314174 DOI: 10.1073/pnas.2536800100]

85 Fevr T, Robine S, Louvard D, Huelsken J. Wnt/beta-catenin is essential for intestinal homeostasis and maintenance of intestinal stem cells. *Mol Cell Biol* 2007; **27**(21): 7551-7559 [PMID: 17785439 PMCID: PMC2169070 DOI: 10.1128/MCB.01034-07]

86 Korinek V, Barker N, Moerer P, van Donselaar E, Huls G, Peters PJ, Clevers H. Depletion of epithelial stem-cell compartments in the small intestine of mice lacking Tcf-4. *Nat Genet* 1998; **19**(4): 379-383 [PMID: 9697701 DOI: 10.1038/1270]

87 Kim KA, Kakitani M, Zhao J, Oshima T, Tang T, Binnerts M, Liu Y, Boyle B, Park E, Emtage P, Funk WD, Tomizuka K. Mitogenic influence of human R-spondin1 on the intestinal epithelium. *Science* 2005; **309**(5738): 1256-1259 [PMID: 16109882 DOI: 10.1126/science.1112521]

564 88 Farin HF, Van Es JH, Clevers H. Redundant sources of Wnt regulate intestinal stem cells and promote formation of Paneth
565 cells. *Gastroenterology* 2012; **143**(6): 1518-1529 e1517 [PMID: 22922422 DOI: 10.1053/j.gastro.2012.08.031]
566 89 Sato T, Vries RG, Snippert HJ, van de Wetering M, Barker N, Stange DE, van Es JH, Abo A, Kujala P, Peters PJ, Clevers H.
567 Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. *Nature* 2009; **459**(7244): 262-265 [PMID:
568 19329995 DOI: 10.1038/nature07935]
569 90 Takashima S, Kadowaki M, Aoyama K, Koyama M, Oshima T, Tomizuka K, Akashi K, Teshima T. The Wnt agonist
570 R-spondin1 regulates systemic graft-versus-host disease by protecting intestinal stem cells. *J Exp Med* 2011; **208**(2): 285-294 [PMID:
571 21282378 PMCID: PMC3039850 DOI: 10.1084/jem.20101559]

572