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Hypothesis

Bitter components related to alleviating intestinal obstruction in traditional Mongolian medicine

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Highlights

Intestinal obstruction is an abdomen disease that keeps digesta from passing through intestine. Surgical interventions will be performed once the diagnosis of strangulated intestinal obstruction or intestinal necrosis is confirmed. However, the mortality rate is alarmingly high after emergent surgery. Traditional Mongolian medicine has been proven to be efficacious in the clinical treatment of intestinal obstruction based on its unique theory on bitter flavor property. Here we assessed the link between functional bitter taste signaling and the treatment of intestinal obstruction. The effectiveness of bitter Mongolian medicine in treating the disease may point to a promising role of the bitter receptor as a target for disease treatment.

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Abstract
Intestinal obstruction is a blockage that keeps digesta from passing through upper or lower intestine. Traditional Mongolian medicine (TMM) has been proven to be efficacious in the clinical treatment of intestinal obstruction. However, the mechanism of its treatment has not been studied. The bitter taste receptors (*T2Rs*) are highly expressed in the extra-oral digestive system, such as gastrointestinal tract, which can regulate gastrointestinal peristalsis and contraction of gastrointestinal smooth muscle. In the respiratory system, T2Rs can relax the airway smooth muscle and effectively alleviate asthma symptoms. In this review, the theory and clinical applications of bitter herbs in TMM were discussed and the functional expression of *T2Rs* and bitter taste signal transduction pathway were analyzed to investigate whether bitter Mongolian medicine may play an effective role in promoting gastrointestinal peristalsis. Therefore, the scientific connotation of the theory of bitter medicinal property of TMM was interpreted by combining *T2Rs* research and application of modern technology. This new research approach may enrich and improve the basic theory and accelerate the modernization of TMM.
Keywords: Intestinal obstruction, Mongolian medicine, Bitter taste receptors, Signal transduction pathway

***Abbreviations*:**

TMM: Traditioanal Mongolian medicine; T2Rs: Bitter taste receptors; TRCs: Taste receptor cells; GPCR: Seven-transmembrane G protein–coupled receptors; TMR: Transmembrane region; ICLs: Intracellular loops; ECLs: Extracellular loops; cAMP: Cyclic adenosine monophosphate; PLCb2: Phospholipase C b2; DAG: Diacylglycerol; TRPM5: Transient receptor potential ion channel subfamily member 5; IP3: Inositol triphosphate; PKA: Protein kinase A.

***Competing interests*:**

The authors declare that there is no conflict of interest.

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Introduction

The obstruction of intestinal contents caused by any reasons are collectively considered as intestinal obstruction [1]. Relevant symptoms include abdominal distension, abdominal pain, abdominal muscle tension, vomiting, defecation and exhaust cessation etc [2,3]. These symptoms are significantly correlated with the location and severity of intestinal obstruction [4]. If the obstruction occurs in the upper intestine, patients may present with violent vomiting, which begins with vomiting food followed by yellow water or mucus. If the obstruction affects the lower part, patients will vomit foul-smelling food, the defecation passage will be closed and the abdominal distension will be aggravated [5].

In Western medicine, intestinal obstruction can be treated by surgical and non-surgical interventions. Routine treatments including gastrointestinal decompression, correction of water and electrolyte disorders and acid-base imbalances can be delivered for simple and incomplete intestinal obstruction. However, once the diagnosis of strangulated intestinal obstruction or intestinal necrosis is confirmed, surgery should be performed immediately [6]. If left untreated, it can lead to death. Singh et al. reported that the mortality rate is alarmingly high after emergent surgery [7]. Therefore, preoperative optimization and effective non-surgical treatment are urgently required to avoid emergent surgery. Although recently nasogastric tube method, anterior balloon method and rectal stents have been widely applied in the treatment of intestinal obstruction, the success rate is merely low and methodologies are physically invasive [8-11]. The basic theory of Traditional medicine in combination with the use of herbal medicine can be considered to treat intestinal obstruction and avoid surgery [12].

Traditional Mongolian medicine (TMM) has its own unique theory to treat intestinal obstruction with medicinal taste and property as its core contents [13]. It is the medication law summarized by the ancestors of Mongolian medicine from long-term clinical and medical practice, which covers the theory of "Arag and Bilig", "Three roots", "Five-phase theory", "Six basic disease theory" and various drug properties and therapeutic effects [14]. Bitter taste is one of the six tastes on the theoretical basis of TMM, which is produced by water and gas elements. It has the basic characteristics of cold, light, blunt and rough, and functions to reduce fat and enhance gastrointestinal motility [15]. At present, although multiple clinical studies have been conducted to investigate intestinal obstruction in TMM, this disease has not been well diagnosed and treated [16, 17]. In this article, research progress on the application of bitter Mongolian medicine in the treatment of intestinal obstruction was reviewed. In addition, the structure expression and signal transduction pathway of bitter taste receptors (T2Rs) were investigated, aiming to evaluate the feasibility of Mongolian medicine in treating intestinal obstruction.

Methods and Hypothesis

1. Diagnostic principles and treatments of TMM for intestinal obstruction

In the basic theory of TMM, three roots (Heyi, Xieri, Badgan) are inherent in human beings. If the relative balance is disrupted, it is likely to provoke pathological changes [13]. Intestinal obstruction is an intestinal emergency in which the Badgan Heyi is excessive and the function of the Heyi is disordered, resulting in the inability of the intestinal contents to pass, also known as "intestinal distortion" [14]. In addition, the incidence of intestinal obstruction is subject to multiple causes. Nevertheless, in TMM, the main causes are the imbalance of three roots and seven elements, the disorder of intestinal heat transfer and the abnormal operation of Heyi, which lead to intestinal obstruction [14]. The intestine is the residence of Heyi and the physiological function and pathology of the large intestine are also dominated by Heyi [16]. According to the principle of opening up Heyi and symptomatic treatment, the Mongolian medicine prescription can be applied to treat intestinal obstruction. Firstly, patients are forbidden to take food and water, and then hot compressed with oil cloth around the abdomen and the 17th vertebral joints. Simultaneously, patients are treated with Amuri-6 decoction, which consists of six kinds of medicinal herbs: TumuXiang (*Radix Inulae*), Shannai (*Rhizoma Kaempeeriae*), Dahuang (*Radix Et Rhizoma Rhei*), Hezi (*Fructus Terminaliae Billericae*), Hanshuishi (*Gypsum Rubrum*) and Jianhua (*Bul Tog*), which functions to strengthen the spleen and stomach, digestion, relieve abdominal distension, moisten intestine and mitigate constipation. In addition, the application of embelia laeta and pomegranate exert the effect on moistening intestine, relieving constipation, and improving pathway. When the symptoms are relieved, the laxative of rhubarb-3 decoction can be administered. After normal defecation and exhaust, soft, digestible and light food can be given. Patients should be free from decay, tobacco and alcohol, raw and cold, greasy, hard, spicy food and avoid intense exercise [16, 17].

2. Bitter compounds in Mongolian medicine for intestinal obstruction

Mongolian medicine Dahuang (*Radix Et Rhizoma Rhei*)

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is bitter in taste and cold in nature. It has the functions of purging, clearing away heat, detoxifying, curing sores and wounds, and digesting food. Dahuang (*Radix Et Rhizoma Rhei*) is mainly applied to treat constipation, abdominal distension, dysfunction of Heyi movement, dyspepsia and other symptoms. Modern studies have demonstrated that anthraquinone, one of the bitterest compounds is the main chemical component of Dahuang (*Radix Et Rhizoma Rhei*) that acts upon the large intestine, and sensenoside A exerts the strongest effect [18]. Liu have employed rhubarb and glauber's salt solution on the basis of conventional treatment, and proposed that it effectively mitigates abdominal pain, vomiting, defecation and exhaust [19]. Dahuang decoction enema treatment can effectively promote gastric peristalsis and alleviate relevant symptoms [20]. Tang demonstrated that Dahuang powder applied to Shenque point combined with abdominal acupoint massage can promote gastrointestinal peristasis and restore intestinal patency [21]. A variety of effective ingredients of rhubarb have been proven to promote gastrointestinal peristalsis, eliminate intestinal paralysis, inhibit intestinal absorption of toxins and promote the elimination of endotoxin. In addition, it can improve human immunity [22,23]. Besides, many Mongolian medicines have been considered to be related to gastrointestinal motility, such as Binlang (*Semen Arecae*) and Chuanxiong (*Rhizoma Chuanxiong*) , etc. Modern pharmacological studies have confirmed that areca catechu also exerts effect on gastrointestinal motility, which can increase gastrointestinal peristalsis and increase gastrointestinal smooth muscle tension [24]. Sun et al. have indicated that Binlang (*Semen Arecae*) can accelerate gastrointestinal motility [25]. Toosendanin is the main chemical constituent of melia toosendanin, which can increase the contractility of in vitro and in situ intestinal muscles in rabbit models. Moreover, it can cause spasmodic contraction of the intestinal muscles at higher concentrations [26]. The simmered melia toosendanin exerts spasmolytic effect upon in vitro intestinal muscles in rabbit models [27]. To sum up, TMM has their own unique theory in the treatment of intestinal obstruction, and medicinal herbs and main active components are classified as bitter taste and exerts improvement on gastrointestinal motility, which plays a potential role in the clinical treatment of intestinal obstruction. More traditionally used bitter medicinal herbs are summarized in Table 1.

Table 1. Characteristics and pharmacological action of commonly usedMongolian medicinal herbs

Mongolian medicine	Taste, nature	Main chemical composition	Pharmacological action	Reference
Dahunag (*Radix Et Rhizoma Rhei*)	Bitter, cold	Anthraquinones	Purgation, weight loss, hemostasis, hypolipidemia, anti-microbial, anti-inflammation, anti-tumor, anti-infection, antipyretic, cholagogue, liver protection, diuresis, improvement of renal function and immune regulation, etc.	[28,29]
Muxiang (*Radix Aucklandlae*)	Bitter, warm	Saussurine	Spasmolysis and analgesia, promoting gastric motility, anti-inflammation, anti-tumor, cholagogue, anti-gastric ulcer, anti-pathogenic microorganisms and effects on cardiovascular system, etc.	[30]
Chuanmuxiang (*Radix Vladimiriae*)	Bitter, warm	Sesquiterpene lactones (costunolide, denydcrostus lactone)	Spasmolysis, liver protection and cholagogue, anti-inflammation, anti-tumor and effect on gastrointestinal tract (promote small intestine movement) , etc.	[31]
Jinqianpu (*Acorus gramineus Soland*)	Bitter, warm	Volatile oil	Effects on the digestive system (inhibition of spontaneous intestinal contraction, intestinal spasm, promoting intestinal peristalsis), nervous system (sedation, anti-convulsion, anti-depression, intelligence, anti-aging), lipid-lowering, bacteriostasis, anti-cancer and carcinogenesis, etc.	[32]

Juemingzi (*Semen Cassiae*)	Less bitter, cool	Anthraquinones	Purgation, reduce blood pressure, hypolipidemia, liver protection, eyesight, bacteriostasis, anti-oxidant, anti-diabetes,anti-tumor and immunization, etc.	[33-37]
Jingdaji (*Radix Euphorblae Pekinensis*)	Bitter, cool	Diterpenes	Purgation, anti-cancer, anti-inflammation, anti-leukemia, toxic effects, etc.	[38, 39]
Sharen (*Fructus Amomi*)	Bitter, hot	Volatile oil	Gastrointestinal protection (Promoting gastric emptying and peristalsis, anti-gastric ulcer),analgesia, anti-inflammation,anti-diarrhea, hypoglycemic, anti-oxidant, bacteriostasis and regulation of flora, etc.	[40]
Binlang (*Semen Arecae*)	Bitter, hot	Arecoline	Promoting gastric motility, Purgation, exterminate snail, drive insect and kill insect, bacteriostasis and cause oral mucosal lesions, etc.	[41]
Chuanlianzi (*Fructus Toosendan*)	Bitter, cool	Toosendanin	Effects on digestive system (Increasing muscle tone), effects on cardiovascular system, respiratory depression, inhibiting osteoclasts, anti-oxidant, anti-botulinum, anti-microbial, diminish inflammation, analgesia and anti-virus, anti-tumor, etc.	[42]
Zhizi (*Fructus Gardeniae*)	Bitter, cool	Iridoids (geniposide)	Purgation, cholagogue, liver protection, lipid-lowering, reduce blood pressure and hpyerglycemic, anti-microbial, diminish inflammation, anti-oxidant, anti-fatigue, anti-thrombotic and promoting pancreatic secretion and neuroprotection, etc.	[43, 44]

3. The signal transduction mechanism of bitter taste receptors

Bitter taste is a self-defence sensing system which relates to the recognition of potential toxic compounds interacting with its cognate *T2Rs*. *T2Rs* belong to the superfamily of seven-transmembrane G protein–coupled receptors (*GPCR*), which are the targets of > 60% of drugs currently on the market [45]. Because bitter compounds have a variety of chemical structures, it is believed that bitter signal transduction pathways exist in different forms. The production of

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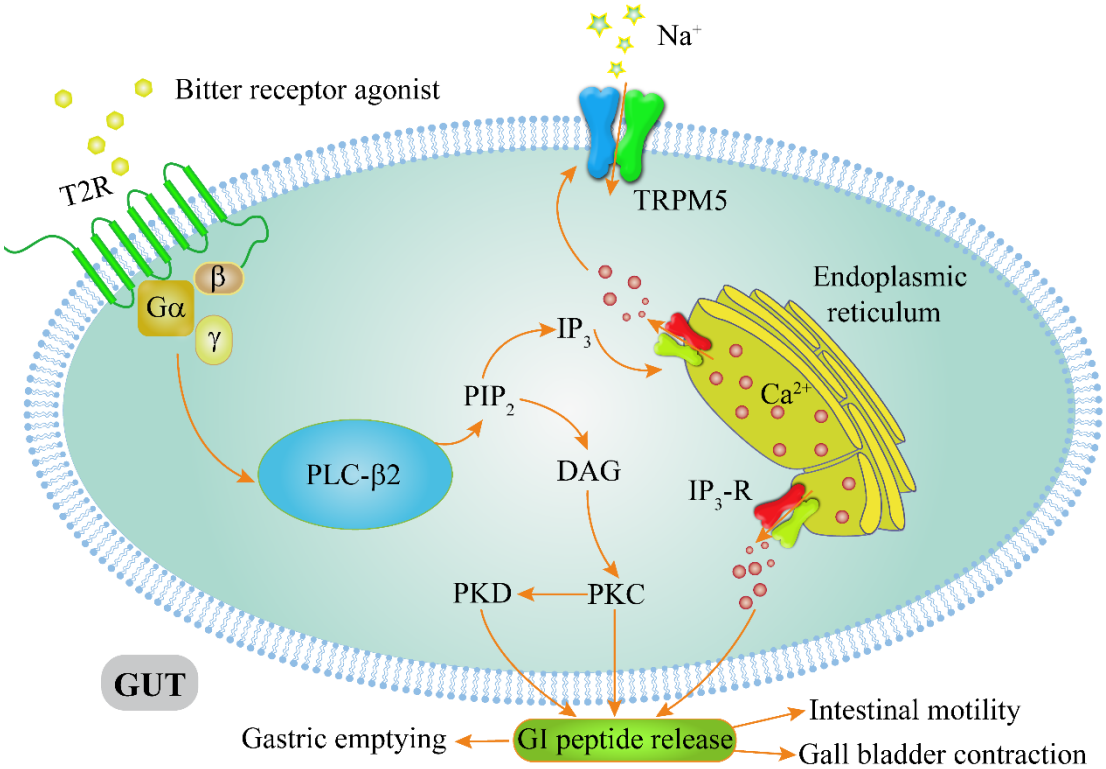
bitter taste mainly has three elements including bitter substances, bitter receptors and ion channels. Studies have demonstrated that G protein plays a pivotal role in the signal transduction pathway of taste cells [46]. G protein is a heterotrimer composed of α - subunit and βγ- subunit [47]. When bitter substance binds to the receptor, it activates the signaling pathway mediated by Ga and Gβγ, thereby producing bitter taste perception (Figure 1).

Figure 1. Bitter taste receptor signalling in the gastrointestinal tract



After *GPCR* activation, the extracellular stimulation can be converted into intracellular signals. Thus, various physiological functions of the organism are regulated by *GPCR*, which is a pivotal drug target [48]. T2Rs are not only expressed in human taste bud cells for sense bitterness, but also expressed in the endocrine, respiratory system and cardiovascular system [49, 50]. It consists of transmembrane region (TMR), intracellular carboxyl-terminal, shorter extracellular amino N-terminal, intracellular loops (ICLs) and extracellular loops (ECLs) [51]. Among them, TMR can separate *T2Rs* into ECls and ICs, which is an important bridge between G protein and activation site [52, 53]. Among the structures of *T2Rs*, the most conserved part is the transmembrane region followed by the intracellular region, the ICLs are intracellular G protein-coupled regions, and the extracellular shorter N-terminal structure can bind to various bitter substances [57]. The combination of a bitter compound with *T2Rs* can elicit a variety of physiological functions, including gastrointestinal motility.

Bitter taste has at least three different transduction pathways [55]. The first is Ga-mediated signaling pathway. Some bitter substances, such as actinomycetes, when combined with T2Rs, will activate the α-subunit, thereby activating phosphodiesterase and leading to decreased intracellular cyclic adenosine monophosphate (cAMP) level and decreased protein kinase A (PKA) activity. The decreased level of cAMP abolishes the inhibitory effect of cAMP on ion channels, opening the $Ca2^{+}$ channel, which in turn leads to increased intracellular $Ca2^{+}$ concentration, depolarization of cell membrane and release of neurotransmitters [56, 57]. The second signaling pathway is mediated by Gβγ. Some bitter substances, such as denatonium benzoate, when combined with T2Rs and activate the βγ-subunit, the release of βγ-subunit activates PLCβ-2, and then activates Phosphatidylinositol Biphosphate (PIP2) and produces diacylglycerol (DAG) and inositol triphosphate (IP3). These events lead to the opening of the $Ca2^{+}$ channel, which in turn induces an increase in intracellular $Ca2^{+}$ concentration that activates the transient receptor potential ion channel subfamily member 5 (TRPM5) channel, causing Na+ influx, which ultimately leads to cell membrane depolarization and neurotransmitter release [58,59]. In addition, certain signal transduction pathways are independent of G protein. By knocking out the Gustducin gene in mice,

it has been found that these mice can still perceive bitterness, indicating that some bitter substances are independent of G protein that can bind directly to bitter receptors and open ion channels. For instance, quinine can shut down K^+ channels and eventually depolarize cell membranes and release neurotransmitters. Some studies have demonstrated that denatonium benzoate decreases the level of cAMP and increases the activity of PLCβ2, which leads to an increase of intracellular $Ca2^+$ concentration and the release of hormone [60]. Therefore, understanding the *T2R* signaling pathways may help to reveal the potential mechanism of TMM in the treatment of intestinal obstruction.

4. Bitter taste receptor in the oral cavity and the gastrointestinal tract

Bitter sensation in the mouth serves sentinel functions to prevent the ingestion of toxins. In the mammalian oral cavity, circumvallate, foliate, fungiform, palate, and epiglottis structures, taste buds conserve taste receptor cells (TRCs) which are selectively expressing *T2R* genes [61-63]. Adler et al showed that a single TRC could express a large repertoire of *T2Rs*, which indicates that each taste cell may be capable of recognizing multiple bitter compounds [61]. The wide-range of expression is consistent with the role of the gustatory system function as a set of broadly tuned sensors for all bitter chemicals which might be unable to discriminate them from one to another. *α-Gustducin*, *a G-protein* subunit in the transduction of bitter taste, is invariably expressed with *T2R* genes in the *TRCs* [64, 65].

Canonically, *T2Rs* are expressed in taste buds of the tongue, where they initiate bitter taste sensation. However, accumulating evidence indicates that *T2Rs* are widely expressed throughout the body and mediate diverse nontasting roles through various specialized mechanisms. The *T2R* family and related signalling molecules have been discovered in the mouse stomach and intestine [66]. The following studies have shown that taste signalling G protein a-gustducin has also been found in the enteroendocrine cell lines [67-70]. Wu et al identified the presence of a-gustducin, a-transducin, and 11 *T2R* genes in the gastrointestinal mucosa and STC-1 cells. They showed bitter agonists (e.g. denatonium, phenylthiocarbamide, 6-n-propil-2-thiouracil, and cycloheximide) stimulate STC-1 cells resulting in a rapid increase of intracellular $Ca2^+$ concentration [70]. Rozengurt et al concluded that bitter agonists mediate depolarization and $Ca2^+$ influx through stimulating the voltage-sensitive ion channels [71]. *T2Rs* that are identified in the oral cavity and the gastrointestinal tract of human and laboratory animals are summarized in Table 2.

Table 2. Expression of T2Rs in the oral cavity and the gastrointestinal tract

System	Tissue or cell type	Species	*T2Rs* expressed (*T2Rx*)
Taste	Taste papillae	Human	1, 3, 4, 5, 7, 8, 9, 10, 13, 14, 16, 19, 20, 30, 31, 38, 39, 40, 41, 42, 43, 45, 46, 50, 60
	Taste papillae	Mouse	102, 103, 104, 105, 106, 107, 108, 109, 110, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 129, 130, 131, 134, 135, 136, 137, 138, 139, 140, 143, 144
Gastrointestinal tract	Stomach/duodenum	Rat	r1, r2, r3, r4, r5, r6, r7, r8, r9, r10, r12, r16, r34, r38
		Mouse	108, 134, 138
	Cecum/colon	Human	3, 4, 5, 9, 10, 13, 20, 30, 31, 38, 39, 40, 42, 43, 46, 50, 60
	NCI-H716 cells	Human	9, 38
	HuTu-80	Human	4, 5, 14, 16, 20, 30, 31, 38, 39, 40, 46, 50, 60
	STC-1 cells	Mouse	108, 134, 135, 137, 138, 144
	Ar42J	Rat	r16, r34, r38

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5. Extended function of T2Rs

Previously, bitter substances are considered to be recognized by *T2Rs*, thus keeping the body away from toxic and harmful substances. In recent years, accumulated evidences indicate that bitter taste receptors are expressed not only in the taste bud cells of the tongue, but also in the cardiovascular system, digestive tract, urinary system, respiratory system, which have specific physiological functions [72]. Studies have demonstrated that certain *T2Rs* are expressed in the airway smooth muscle, which can relax the smooth muscle after being stimulated by the bitter agent and effectively alleviate the symptoms of asthma. It is also expressed in the intestinal endocrine cells of rats, the gastric and fundus mucosa of mice, and the inner wall of duodenum [73-75]. Gastrointestinal tract is considered to be the second brain of the human body, also known as the "intestine brain", which is not only the largest and most complex endocrine system of the human body, but also the largest immune organ [76]. In addition, modern pharmacological studies have confirmed that bitter Chinese medicine can regulate gastrointestinal peristalsis, relieve gastrointestinal smooth muscle, and affect gastrointestinal hormone secretion and intestinal mucosal growth [77]. Besides, Singh et al. have detected the expression levels of *T2R104*, *T2R108* and *T2R138* in cultured C6 glial cells and mouse brainstem, cerebellum, cortex and nucleus accumbus by RT-PCR [78]. Recent researchers have found that the expression of *T2R5* in the testis of transgenic mice [79]. Currently, it has been confirmed that human body has 25 *T2Rs*, which are mainly distributed on chromosome 5,7 and 12 [80,81]. In contrast, the number of *T2Rs* varies considerably from species to species. For example, mice and pigs have 35 and 23 *T2Rs* while chickens only have 3 *T2Rs*, possibly due to their environmental niches and the feeding behaviour [82- 84].

In summary, it can be inferred that the bitter taste compound binds to the bitter taste receptor of each organ, which is associated with multiple physiological functions. Although few studies have directly assessed the link between bitter taste signaling and the treatment of intestinal obstruction, the effectiveness of bitter taste Mongolian medicine in treating the disease points to a promising role of the bitter receptor as a target for disease treatment.

Conclusion

Taken together, intestinal obstruction is one of the common abdomen diseases that keeps digesta from passing through intestine. If not timely treated, it will lead to intestinal necrosis and abdominal infection. Mongolian medicine has its own unique theory on diagnosis and has been proven to be efficacious in the clinical treatment using bitter Mongolian prescriptions such as Amuri-6 decoction and Rhubarb-3 decoction. However, the therapeutic mechanism has not been thoroughly studied. In this article, the theory and application of the bitter property of Mongolian medicine on treating intestinal obstruction were summarized, and the potential mechanisms has been inferred based on the bitter taste receptor molecular and signaling pathway. This hypothesis may improve and enrich the theory of Mongolian medicine, accelerate the modernization of TMM and widen it's clinical application.

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