สมุนไพรเพื่อใช้รักษาอาการอุจจาระร่วง: จากวิทยาศาสตร์พื้นฐานสู่การประยุกต์ใช้ทางคลินิกแพทย์แผนไทย

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บทคัดย่อ

อุจจาระร่วงเกิดจากการเคลื่อนไหวที่เพิ่มขึ้นร่วมกับเพิ่มการหลั่งและลดการดูดซึมของน้ำในท่อทางเดินอาหาร ทำให้เกิดการสูญเสียน้ำและอิเล็กโทรไลต์โดยเฉพาะโซเดียม ดังนั้น การขาดน้ำและความไม่สมดุลของกรดด่างในร่างกายจึงเป็นภาวะที่อันตรายในอุจจาระร่วงเฉียบพลัน การรักษาที่สำคัญเป็นอันดับแรกเพื่อช่วยลดการตายคือ การทดแทนด้วยสารน้ำและอิเล็กโทรไลต์ โดยให้ดื่มสารน้ำทดแทนทางปากซึ่งประกอบด้วยโซเดียม คลอไรด์ กลูโคส และโพแทสเซียม ยาที่ใช้รักษาอุจจาระร่วงได้ดีควรมีคุณสมบัติ 1) ลดออสโมลาริตีในท่อทางเดินอาหาร 2) ลดการหลั่งและเพิ่มการดูดซึมอิเล็กโทรไลต์ และ 3) ลดการเคลื่อนไหวของท่อทางเดินอาหาร ส่วนการรักษาด้วยยาฆ่าเชื้อเหมาะสำหรับผู้ป่วยที่ทราบชนิดของเชื้อโรคชัดเจน อย่างไรก็ตาม ยาหลายชนิดมีฤทธิ์ไม่พึงประสงค์และการใช้ยาฆ่าเชื้อเกินความจำเป็นยังก่อให้เกิดภาวะเชื้อดื้อยา สมุนไพรจึงเป็นอีกทางเลือกหนึ่งในการรักษาเพื่อช่วยลดฤทธิ์ไม่พึงประสงค์จากยาแผนปัจจุบัน องค์การอนามัยโลกแนะนำสมุนไพรกว่า 5,000 ชนิดที่ใช้รักษาอุจจาระร่วง การศึกษาพืชสมุนไพรหลายชนิดพบว่ามีสารที่ออกฤทธิ์ช่วยลดการเคลื่อนไหวและ/หรือการหลั่งในท่อทางเดินอาหาร การรักษาของแพทย์แผนไทยใช้พืชที่มีความเป็นกรดและมีรสฝาดเพื่อช่วยลดการหลั่งน้ำในท่อทางเดินอาหาร โดยพืชสมุนไพรอาจใช้เป็นชนิดเดียวหรือใช้ร่วมกันหลายชนิด งานวิจัยที่ศึกษาประสิทธิภาพของสมุนไพรแสดงให้เห็นว่าการใช้พืชสมุนไพรร่วมกันหลายชนิดได้ผลในการรักษาดีกว่าการใช้เพียงชนิดเดียว ตัวอย่างพืชและสมุนไพรที่ใช้รักษาอุจจาระร่วงในไทย เช่น ทับทิม ฝรั่ง สีเสียดเหนือ มังคุด กล้วยน้ำว้า ฟ้าทะลายโจร ยาเหลืองปิดสมุทร ยาธาตุบรรจบ

คำสำคัญ: อุจจาระร่วง สมุนไพร การรักษาแพทย์แผนไทย

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Medical plants treatment for diarrhea: from basic science to Thai traditional clinical application

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Abstract

Diarrhea is a symptom involves both an increase in the motility of the gastrointestinal tract along with increased secretions and a decrease in the absorption of fluid. Thus a loss of water and electrolytes particularly Na^+ are occurred. Dehydration as well as electrolyte and acid-base imbalance is critical condition during acute diarrhea. The most importance and primary therapy to reduce mortality is the replacement of water and electrolytes. Oral rehydration therapy is the replacing lost fluids and electrolytes with oral rehydration solution (ORS) which containing sodium, chloride, glucose and potassium. An ideal antidiarrheal drugs should have the ability to reverse 1) the increased luminal osmolarity of osmotic diarrhea, 2) the increased electrolyte secretion of secretory diarrhea, 3) the decreased electrolyte absorption and 4) the deranged intestinal motility that causes a decreased in transit time. Antibiotics are recommended for diarrheal patients who identified enteric pathogen. However, many antidiarrheal drugs possess various adverse effects as well as the overuse of antibiotics has become the major factor of multi-drug resistant strains of microorganism. Herbal remedies are alternative treatment that possessed lesser adverse effects than the conventional drugs. The World Health Organization (WHO) has catalogued more than 5,000 of medicinal plants which are used to treat diarrhea. Many plants possess antidiarrheal activity, which act by reducing the gastrointestinal motility and/or the secretions. In Thai traditional treatment, the treatment of diarrhea involves the use of acidic and astringent ingredients to decrease the watery excretion. A plant may be used by itself or as a base ingredient in combination with other herbs. Research probing into the efficacy of herbal medicine indicates that an herbal medicine derived from a combination of plants is more effective than that formulated with a single herb. Examples of the plants and herbs administration against diarrhea in Thailand are *Punica granatum* L., *Psidium guajava* Linnaeus, *Acacia catechu* Willd, *Garcinia mangostana* Linn., *Musa spientum* L., *Andrographis paniculata* (Burm.f.) Wall.ex Nees., Ya Lueang Pit Samut and Ya That Banchop.

Keywords: diarrhea, medical plant, Thai traditional treatment

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Diarrhea situation

Diarrhea has been a major of health problem in developing countries especially tropical countries.[1] Acute diarrheal infection is a common health problem globally. It also happened to developed countries individuals traveling to developing countries due to inadequate sanitation and poor hygiene of those localities. The Centers for Disease Control and Prevention has estimated 47.8 million diarrheal cases occurring annually in the United States, at an estimated cost upwards of US$150 million to the health-care economy.[2,3]

Functional anatomy and physiology of intestine

Both small and large intestines are most critical organ in gastrointestinal (GI) tract when it comes to diarrhea. Small intestine is consists of duodenum, jejunum, and ileum. The main function of the small intestine is food digestion and absorption due to its microvilli structural features. The carbohydrate, protein and fat are completely broken down at duodenum. All nutrient including water, electrolyte, vitamin and mineral are absorbed into the blood when the chyme is moved along the intestine. Small intestine does its job with two pathways for intestinal absorption. The first one is transcellular pathway. In this pathway substance must cross the apical membrane into epithelial cell and come out the basolateral membrane to the blood capillary. The second one is paracellular pathway, where substances must travel the tight junction between the intestinal epithelium into interstitium then get into the blood stream.

Across apical membrane, Na^+ gradient is the driving force for many substances, including amino acid, oligopeptide, and sugar to be transported. As these organic solutes are absorbed, salt is absorbed with them. Water then gets osmotically transported from enterocyte to lateral intercellular space, thus a local osmotic gradient that initiates water flow is created. Therefore the coupled transport of Na^+ and organic solutes is the theoretical basis for oral rehydration therapy in severe diarrhea cases.[4]

NaCl absorption in each part of the intestine has a unique mode of transport mechanism. In the apical membrane of jejunum mainly, $NaHCO_3$ is absorbed via Na^+/H^+ exchanger isoform 2 (NHE2) and 3 (NHE3). In apical membrane of ileum and proximal colon, NaCl is absorbed via equal rates of Na^+/H^+ (NHE2 and NHE3) and Cl^-/HCO_3^- exchangers (also called downregulated in adenoma (DRA)) and putative anion transporter 1 (PAT1)[5] (Figure 1).

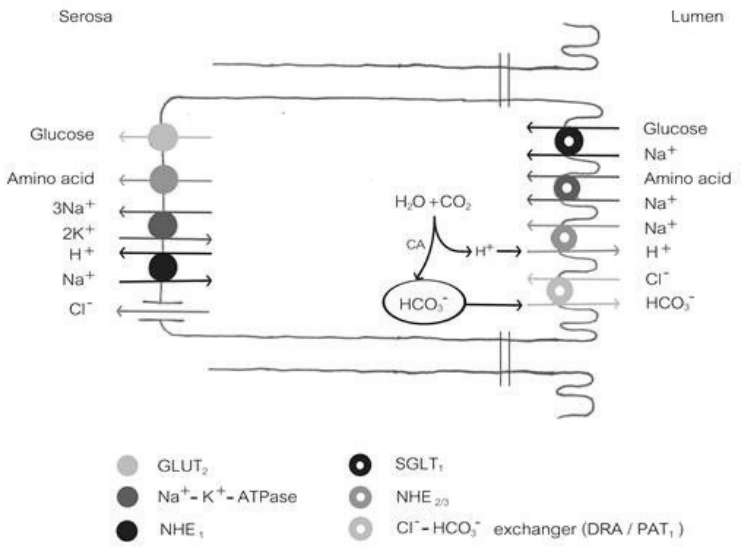

Figure 1 Cellular mechanism of NaCl absorption by the intestine

Chloride absorption and secretion has a role in diarrhea due to the apical Cl^--HCO_3^- exchanger involved in electroneutral NaCl absorption in small intestine. The congenital absence of Cl^--HCO_3^- exchangers causes congenital chloride diarrhea or chloride losing diarrhea.[6] Cystic fibrosis transmembrane conductance regulator (CFTR) regulates the secretion of Cl^-, HCO_3^-, and smaller amounts of other anions in the apical membrane of small intestine. Chloride secretion establishes a lumen-negative electrical driving force for trans-epithelial sodium secretion via the paracellular pathways. Together, Na^+ and Cl^- 's transport into the luminal compartment generates the osmotic driving force for water flow that yields an isotonic secretory product. CFTR normal function of Cl^- secretion contributes to salt and water secretion in small intestine. Chloride transport via CFTR plays a key role in the amplified response observed in secretory diarrheas. Example those are diarrheas elicited by cholera toxin during *Vibrio cholerae* infection or by heat-stable enterotoxin from pathogenic *Escherichia coli* infection[7] (Figure 2).

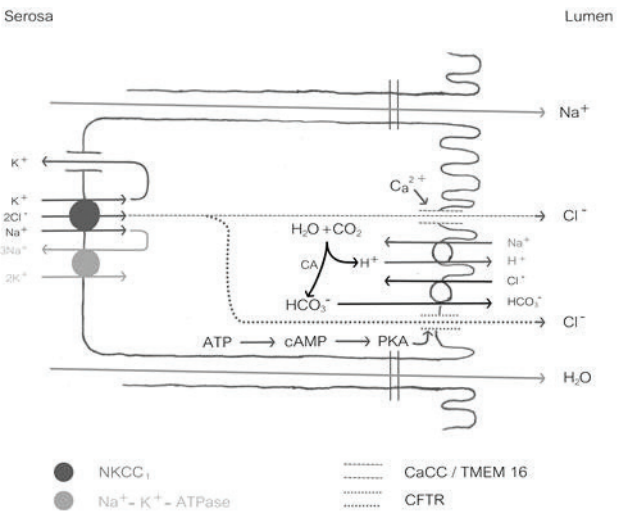

Figure 2 Cellular mechanism of chloride secretion by the intestine

The GI tract absorbs not only nutrients, but also vast amount of electrolytes and fluid. Both small and large intestine absorb approximate 9 liters of fluid daily. The fluid that is not absorbed (100-200 ml) is excreted in feces. It is not surprising that abnormal absorption of fluid in intestine causes diarrhea. In retrospect, severe diarrhea causes an enormous fluid and electrolyte loss. That is the reason why many acute diarrhea cases without replacement therapy end in death, especially in infant and the elderly who has decline homeostatic mechanism.

The main function of the large intestine is defecation. The stool or feces is a solid waste in the lumen of large intestine. It is an unabsorbed portion of the chyme, including some secreted electrolyte and other substances. The large intestine contains microorganism (normal intestinal flora) which have a minor role in completing the digestion of the nutrients.

Beside the digestion of food and absorption of nutrient, one of the major functions of the GI tract is the motility to propel the chyme. There are different specific types of motility in each GI organ, namely segmentation movement in small intestine and huastral and mass movements in large intestine. Segmentation movement is a slow contraction of circular muscle leading to move chyme backward and forward. Such movement mixes the chyme with the pancreatic juice and bile and ensures adequate exposure of chyme to the intestinal wall for absorption. The huastral movement makes the chyme exposed all surfaces to the wall for water absorption. The series of mass movement trigger defecation reflex.

An underlying mechanism of all GI motility is the smooth muscle contraction. There are two types of muscle in intestinal wall; circular and longitudinal muscle (Figure 3). The intestinal smooth muscle cell

is pacing its own contraction similar to cardiac pacemaker cell. Although the contraction is independent to nerve innervation, it is potentially affected by autonomic nervous system. The contraction of intestinal motility is regulated by enteric nervous system in the GI tract and hormone.[8] Parasympathetic stimulation increases the GI motility, but stimulation of sympathetic nerve is known to decrease GI motility. The enteric nervous system directs all functions of the GI tract, even in the absence of extrinsic innervation. The enteric nervous system regulates GI function via its of myenteric and submucosal plexuses (Figure 4).

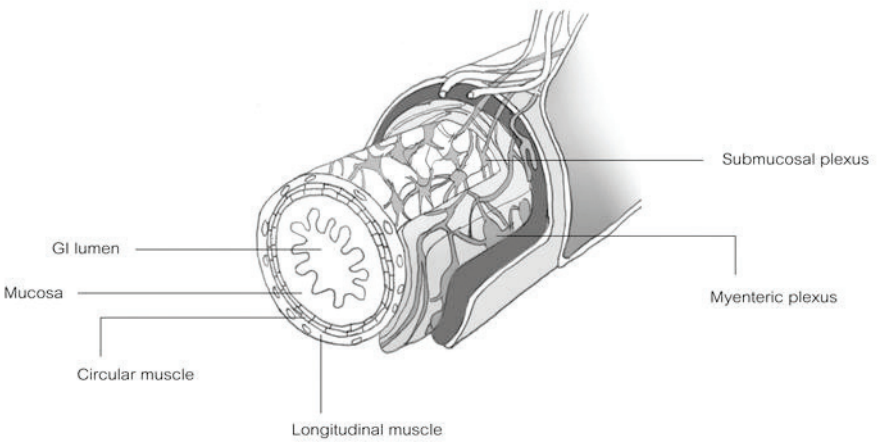

Figure 3 Types of smooth muscle in intestinal wall; circular and longitudinal muscle

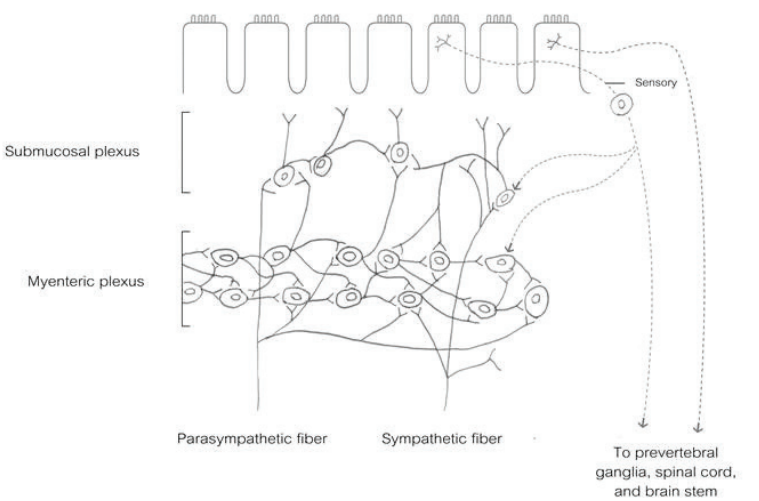

Figure 4 The enteric nervous system regulates GI function via its of myenteric and submucosal plexuses

Pathophysiology of diarrhea

Diarrhea is the increased frequency, volume and fluidity of stool. Diarrheal disease referred to daily stool weights greater than 200 g.[9] Diarrhea symptoms are passing loose, watery stools more often than three times a day, or passing mucous stools more often than once a day. Diarrhea can further cause dehydration, thirst, and exhaustion in patients, especially if the excretion takes place many times, or accompanied by fever, stomachache, flatulence, and nausea. Even though there are many causes of diarrhea, the most important cause of diarrheal death around the world is from infection. There are several chains of events before enteric organism successfully causes diarrhea. Some organisms are not invasive but secrete toxins which stimulate fluid secretion. They are *Vibrio cholera*, pathologic *Escherichia coli*, and rotavirus. Meanwhile the other invades and destroys intestinal epithelium such as *Shigella*, *Salmonella*, *Yersinia*, and *Campylobacter*. The pathophysiology of fluid loss via defecation is caused by several mechanisms. There are three different pathophysiological conditions of diarrhea namely osmotic, secretory, and motile diarrhea.

Osmotic diarrhea is the condition with is nonabsorbable osmolyte substance in the lumen. The nonabsorb osmolyte draws water into the stool. Examples of osmotic diarrhea are lactase deficiency, excessive sorbitol or fructose intake and abuse of lactulose of milk of magnesia. Osmotic diarrheal stool has small volume (less than 500 ml/day) with high fecal osmolality.

Secretory diarrhea is a result of excessive water and electrolyte secretion in luminal gut. It is caused by bacterial toxin, local irritation substance (GI hormones and drug), tumor that produce cholecystokin or secretin. There are many examples of the secretory diarrhea. There are 1) Gastroenteritis from *Escherichia coli*, *Campylobacter*, *Shigella*, *Salmonella*, rotavirus, abuse of stimulant laxatives, 2) Tumor; colon cancer, intestinal lymphoma, pancreatic carcinoma 3) Inflammatory bowel disease 4) Radiation enteritis. The stool characteristics of the secretory diarrhea are large volume (more than 500 ml/day), high electrolyte concentration, blood or excess mucus content. Cholera is a hallmark of secretory diarrhea caused by *Vibrio cholera* infection. *Vibrio cholerae* causes clinical disease by producing an enterotoxin that promotes the secretion of fluid and electrolytes into the small intestinal lumen.

In **motile diarrhea**, increased intestine motility stimulated by inflammation, neuropathy, or obstruction is the cause. The examples of motile diarrhea are 1) fecal impaction 2) early or partial bowel obstruction 3) Irritation bowel syndrome 4) abuse of stimulant laxative 5) excessive caffeine intake 6) malabsorption syndromes, and 7) ischemia bowel syndromes.

Treatment of diarrhea

Diarrhea is classified into acute and chronic diarrhea. Acute diarrhea occurs in less than 4 days. It is predominantly caused by infection, food intolerance, or drug. Chronic diarrhea is considered when the symptoms persist for 3 or more weeks in children or adults and 4 weeks or more in infants. Acute diarrhea of infectious etiology is associated with many clinical features including nausea, vomiting, abdominal pain, bloating, fever, passage of bloody stools, and fecal urgency.[10] It is self-limited and need no treatment. However, acute diarrhea is particularly serious in infant, young children, person who suffer from other illness, and the elderly. The critical causes of death during acute diarrhea are dehydration as well as electrolyte and acid-base imbalance. The most importance and primary therapy to reduce mortality is the replacement of water, electrolyte, and nutrient. Oral rehydration therapy is the replacing lost fluids and electrolytes with oral rehydration solution (ORS) which containing sodium, chloride, glucose anhydrous and potassium citrate. Loperamide and diphenoxylate HCl are commonly used to decrease gastrointestinal motility. Kaolin and pectin are unabsorbents which those adsorb irritants and toxins from the bowel. Antibiotics are reserved for diarrheal patients who identified enteric pathogen. The antibiotics (e.g. levofloxacin, ciprofloxacin, ofloxacin) were recommended for acute infectious diarrhea treatment.[11] An ideal antidiarrheal drug should have the ability to reverse 1) the increased luminal osmolarity of osmotic diarrhea, 2) the increased electrolyte secretion of secretory diarrhea, 3) the decreased electrolyte absorption, and 4) the deranged intestinal motility that causes a decreased in transit time.[12]

Medical plant extracts treatment of diarrhea

Many drugs possess various adverse effects, for example dry mouth, nausea, constipation and headache. Various herbal remedies were studied to see if they possessed lesser adverse effects than the conventional drugs. Antibiotics are sometimes has adverse effects on host such as hypersensitivity, immune-suppression and allergic reaction.[13] Moreover, the overuse of antibiotics has become the major factor of multi-drug resistant strains of microorganisms.[14-16] The World Health Organization (WHO) has catalogued more than 20,000 plants species with medical properties to treat many diseases and five thousand of which are used to treat diarrhea.[17] Many plants possessing anti-diarrheal activity, which act by reducing the gastrointestinal motility and/or the secretions.[18] The main chemical constituents in plants found to be responsible for anti-diarrheal activity are usually tannins and tannic acid, flavonoids, alkaloids, sesquiterpenes, diterpenes, terpenes and terpenoids.[19]

The effect of medical plants used against diarrhea in Thai Traditional Medicine (TTM)

The clinical use of medicinal plants in TTM generally takes the form of administering a concoction made from several plants to the patient. A single plants administration is seldom used. The objective is to alleviate or remove the symptom of illness and to restore physiological balance of the body.[20] In this review we focused in of the Thai medical plant usage for the treatment of diarrhea including *Punica granatum* L., *Psidium guajava* Linnaeus, *Acacia catechu* Willd, *Garcinia mangostana* Linn., *Musa sapientum*, *Andrographis paniculata*. Furthermore, two Thai remedies for diarrhea treatment, Ya Lueang Pit Samut and Ya That Banchop are included in this review.

***Punica granatum* L. (ทับทิม)** is known as pomegranate. Almost all parts of pomegranate are used in traditional medicine to treat various diseases such as infection, ulcer, and diarrhea due to their properties i.e. antioxidant and anti-inflammation.[21] The ellagitannin punicalagins is published as the primary constituent responsible for antibacterial effect.[22] Concerning about anti-diarrheal therapeutic effect, many studies revealed that the simple of extracts of pomegranate hull have efficacy against the virulent intestinal bacteria *Salmonella typhi*[23] and *Vibrio cholera.*[24] An ethanolic extract of *Punica granatum* was shown to be an effective treatment for *E.Coli* O157:H7 infection based on bacteriostatic and bacteriocidal mechanism.[25]

***Psidium guajava* L. (ฝรั่ง)** is a guava tree. The leaves have been used in folk medicine to treat diarrhea, stomachache and hepatic problems. The phytochemical investigations showed that the therapeutic constituents isolated from leaves of guava are flavonoids, especially quercetin. The flavonoids have demonstrated antibacterial activity. Quercetin relaxed intestinal smooth muscle and inhibited bowel contractions. In addition, other flavonoids and triterpenes in guava leaves show antispasmodic activity.[26] Methanol and ethanol extract of guava leaf have inhibitory effects against *Staphylococcus aureus* and *Bacillus cereus* but no effect against *Escherichia Coli* and *Salmonella enteritidis*.[27] A double-blind clinical study on guava leaf showed a decrease in duration of abdominal pain. It is attributed to antispasmodic effect of quercetin present in leaf extract.[28]

***Acacia catechu* Willd (สีเสียดเหนือ)** has been used in Asian traditional medicine for the treatment of several gastrointestinal ailments diseases. Recently, the antidiarrheal effects of *A. catechu* bark extract were studied in Guinea pigs.[29] The results clearly demonstrated that the *A. catechu* bark reduced frequency and amplitude of colon smooth muscle spontaneous contractility. The study demonstrated that *A. catechu* bark has clinical benefits in patients suffering from nonbacterial diarrhea. The mechanism of its spasmolytic and antispastic activities has not yet been elucidated.

***Garcinia mangostana* Linn. (มังคุด)** The pericarp of *G. mangostana* has long been used as an Asian traditional medicine for the treatment of abdominal pain, diarrhea, dysentery, infected wound, suppuration, and chronic ulcer for centuries.[30] Its main biological effects are antioxidant, antitumor, anti-inflammatory and anti-allergy, antibacterial, antifungal, and antiviral properties. *G. mangostana* pericarp extract is a good drug of choice for its antibacterial activity.[31] However, there are a few scientific studies in the antidiarrheal effect of this plant.

***Musa sapientum* (กล้วยน้ำว้า)** Various parts of *M. sapientum* i.e., leaves, root, and flowers have been reported with medicinal properties. Many studies of animal model suggested that *M. sapientum* has ability to ameliorate hypertension, migraine, various human cancer, diarrhea, cholesterol and diabetes.[32] Starch form *M. sapientum* raw fruit chip was found to reduce the severity of diarrhea in critically ill tube-fed patients. Study concluded that *M. sapientum* raw fruit chip can be used as a safe, cost-effective treatment for diarrhea.[33]

***Andrographis paniculata* (Burm. f.) Wall. ex Nees (ฟ้าทะลายโจร)** is widely used in Asian traditional medicine for treating many diseases. The extract of this plant exhibit various pharmacological activities such as immunostimulatory, antiviral, and antibacterial. As major active constituent, andrographolide exhibits a broad range of biological activities, such as anti-inflammatory, antibacterial, antitumor, antidiabetic, antimalarial, and hepatoprotective.[34] This plant is used in the treatment of bacillary dysentery, colitis, and diarrhea of microbial origin. The extract of *Andrographis paniculata* is not only inhibited *Escherichia coli* enterotoxin-induced secretory diatrrhea, but also decreased/increased motility of gastrointestinal smooth muscle which depend on concentration and dose of the extract.[35]

Ya Lueang Pit Samut (ยาเหลืองปิดสมุทร) is a concoction on the National List of Essential Medicines (National Drug System Development Committee, 2012) used to treat the non-infection diarrhea in Thai folk medicine. It composed of 14 different Thai of herbal plants those can easily found around the household. Twelve of those listed in the recipe were report to have gastrointestinal effects and anti-diarrheal activity.[36] Some ingredients of Ya Lueang Pit Samut are found to have antimicrobial activities. Thirty three percent by weight of Ya Leung Pit Samut is composed of *Curcuma longa* Linn. Tumeric oleoresin is known to be beneficial in wound healing and anti-inflammatory processes.[37] Oral feeding of tumeric was reported to enhance gut mucosa by upregultaed neutrophil recruiting genes, the complement system and its regulatory proteins, cytokines IL15 and TNFSF10 and antigen processing and presentation genes.[38]

Ya That Banchop (ยาธาตุบรรจบ) is a drug on the National List of Essential Medicines (List of Herbal Medicinal Products,

2012) used to treat gastrointestinal symptoms, including diarrhea. Ya That Banchop is consumed in the form of capsules, powder, or boluses. The aqueous excipients for Ya That Banchop are infusions prepared from crushed garlic cloves or basil. Boiled water may be used instead in the event that it is impossible to make or find an aqueous excipient. The administration of Ya That Banchop together with anticoagulants and antiplatelets is the caution. Due to toxicity caused by the accumulation of *Cinnamomum camphora* (L.) Presl., prolonged use of the medicine should be under careful supervision, especially among patients with liver and kidney illnesses.

Conclusion

Diarrhea is a worldwide health problem especially in the developing countries. The most common cause of diarrhea is infection. Antibiotic and vaccine in modern medicine has limitation for diarrheal treatment and prevention. Medicinal plants have long been used as traditional treatment of diarrhea. Herbal supplements either as single herbs or as a concoction are widely used in the treatment of diarrhea successfully, although most mechanisms of action are poorly understood. Many animal-based studies have been used to investigate the effect of medicinal plants on the GI function against diarrhea. There is a need to study cellular and molecular effect of Thai medicinal plants in this aspect of both single dose (one medical plant) and herb-herb interaction (combination of medical plants). The result of the research will be beneficial and allow the knowledge to be used to care for the patients with total acceptance.

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