ผลของฟรักโทโอลิโกแซ็กคาไรด์ต่อภาวะท้องผูกในผู้ป่วยเด็ก ณ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี

นางสาวพัชรินทร์ วิจิตรเวียงรัตน์

EFFECT OF FRUCTOOLIGOSACCHARIDES ON CONSTIPATION IN PEDIATRIC PATIENTS
AT QUEEN SIRIKIT NATIONAL INSTITUTE OF CHILD HEALTH

Miss Patcharin Wichitweingrat

A Thesis Submitted in Partial Fulfillment of the Requirements

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พัชรินทร์ วิจิตรเวียงรัตน์ : ผลของฟรักโทโอลิโกแซ็กคาไรด์ต่อภาวะท้องผูกในผู้ป่วยเด็ก ณ สถาบัน สุขภาพเด็กแห่งชาติมหาราชินี. (EFFECT OF FRUCTOOLIGOSACCHARIDES ON CONSTIPATION IN PEDIATRIC PATIENTS AT QUEEN SIRIKIT NATIONAL INSTITUTE OF CHILD HEALTH) (อ. ที่ปรึกษาวิทยานิพนธ์หลัก) : ผศ.ดร. สุญาณี พงษ์ธนานิกร, 146 หน้า.

การวิจัยนี้เป็นการศึกษาแบบ randomized prospective parallel trial เพื่อศึกษาประสิทธิผลของฟรักโท โอลิโกแซ็กคาไรด์ต่อผู้ป่วยเด็กท้องผูกเรื้อรังในช่วงอายุ 4-12 ปี ณ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี จำนวน 54 คน ซึ่งแบ่งออกเป็น 2 กลุ่มคือ กลุ่มที่ได้รับการรักษาด้วยมิลค์ออฟแมกนีเซีย 2.4 กรัมต่อวัน และกลุ่มที่ได้รับ การรักษาด้วยฟรักโทโอลิโกแซ็กคาไรด์ปริมาณ 5 กรัมต่อวัน เป็นระยะเวลา 6 สัปดาห์ โดยกลุ่มตัวอย่างทั้งสอง กลุ่มได้บันทึกรูปแบบการถ่ายอุจจาระก่อนและหลังการรักษา บันทึกการถ่ายอุจจาระและอาการข้างเคียงที่เกิดขึ้น ในแต่ละวันตลอดระยะเวลาการศึกษา บันทึกการรับประทานอาหารย้อนหลัง 24 ชั่วโมงก่อนเข้าร่วมงานวิจัย และ บันทึกการรับประทานอาหาร 3 วันในสัปดาห์สุดท้ายของการรักษา เพื่อนำมาคำนวณพลังงานที่ได้รับจาก สารอาหาร (โปรตีน คาร์โบไฮเดรต และไขมัน) ปริมาณใยอาหาร และน้ำที่ได้รับต่อวัน รวมทั้งมีการประเมินภาวะ โภชนาการของผู้ป่วยโดยการชั่งน้ำหนักและวัดส่วนสูงทั้งหมด 3 ครั้ง คือ เมื่อเริ่มการการทดลอง และหลังได้รับ การรักษา 2 และ 6 สัปดาห์

ผลของการรักษาด้วยฟรักโทโอลิโกแซ็กคาไรด์ในผู้ป่วยเด็กท้องผูกเรื้อรัง พบว่าจำนวนครั้งในการถ่าย อุจจาระต่อสัปดาห์เพิ่มขึ้น ลักษณะอุจจาระนิ่มขึ้น ไม่มีการเบ่งถ่ายอุจจาระ รวมทั้งไม่พบการเจ็บปวดและอุจจาระ มีเลือดปนขณะถ่ายอุจจาระ เมื่อเปรียบเทียบกับก่อนรักษาอย่างมีนัยสำคัญ ($p < 0.001$) ก่อนการรักษาพบว่า รูปแบบการบริโภคอาหารของทั้งสองกลุ่มไม่แตกต่างกัน หลังการรักษาพบว่ากลุ่มที่ได้รับมิลค์ออฟแมกนีเซียมี ปริมาณโปรตีนและไขมันที่ได้รับต่อวันมากกว่ากลุ่มที่ได้รับฟรักโทโอลิโกแซ็กคาไรด์ ($p = 0.046$ และ 0.039 ตามลำดับ) นอกจากนี้พบว่าสัดส่วนการบริโภคใยอาหารเพิ่มขึ้นในทั้งสองกลุ่มเมื่อเปรียบเทียบกับก่อนการ รักษา กลุ่มตัวอย่างทั้งหมดมีภาวะโภชนาการปกติ แสดงว่า การรักษาด้วยฟรักโทโอลิโกแซ็กคาไรด์ไม่ส่งผล รบกวนการเจริญเติบโต สำหรับประสิทธิผลของการรักษาด้วยฟรักโทโอลิโกแซ็กคาไรด์ต่อภาวะท้องผูกไม่ แตกต่างกับการรักษาด้วยมิลค์ออฟแมกนีเซีย ($p = 0.361$) พบว่าร้อยละ 24 ของกลุ่มตัวอย่างมีอาการข้างเคียงจาก การได้รับฟรักโทโอลิโกแซ็กคาไรด์ ได้แก่ ปวดท้อง ท้องอืด ผายลม และคลื่นไส้ ซึ่งอาการที่เกิดขึ้นนี้ไม่รุนแรง จากผลการวิจัยแสดงให้เห็นว่าฟรักโทโอลิโกแซ็กคาไรด์สามารถเป็นอีกแนวทางหนึ่งในการรักษาผู้ป่วยเด็ก ท้องผูกเรื้อรังได้

ภาควิชา............อาหารเคมี.. ลายมือชื่อนิสิต..
สาขาวิชา..อาหารเคมีและโภชนศาสตร์ทางการแพทย์.. ลายมือชื่อ อ. ที่ปรึกษาวิทยานิพนธ์หลัก............................
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    PROF. SUYANEE PONGTHANANIKORN, Ph.D., 146 pp.

This randomized prospective parallel trial was conducted to determine the efficacy of fructooligosaccharides (FOS) on chronic constipation in 4-12 year-old pediatric patients at Queen Sirikit National Institute of Child Health (n = 54). The subjects were divided into 2 groups. The first group was treated with 2.4 grams of milk of magnesia (MOM) per day and the other group was treated with 5 grams of FOS per day for the duration of 6 weeks. All subjects performed defecation pattern record before and after treatments and also recorded defecation and adverse effects during receiving the treatments. Dietary intake at the beginning and the last week of the treatments were assessed by 24-hour recall and 3-day food record respectively to determine total energy, protein, carbohydrate, fat, dietary fiber, and water intakes per day. In addition, nutritional status of the subjects were assessed 3 times of visit (at baseline, week 2 and week 6 of the treatments) by weight and height measurements

Results of FOS treatment in constipated pediatric patients showed a significant increase in the stool frequency, improvement of stool consistency, no straining, no pain at anus and blood-streaked stool during defecation when compared with baselines ($p < 0.001$). Dietary patterns of the subjects in the FOS and MOM groups at the beginning of the study were not significantly different. After the intervention, the amount of protein and fat intakes in the MOM group were significantly greater than those in the FOS group ($p = 0.046$ and 0.039 respectively).   The proportion of dietary fiber intake in the FOS and MOM groups increased after the treatments compared to baseline. The nutritional status of all subjects was in normal range. It indicated that FOS did not interfere the growth status. The efficacy in treatment of constipation with FOS and MOM were not significantly different ($p = 0.361$). Twenty-four percent of the subjects treated with FOS suffered from adverse effects including abdominal pain, flatulence, flatus, and nausea; however, these effects were not serious. This study indicated that FOS could be an alternative choice to treat chronic pediatric constipation.

Department ...Food Chemistry……………………….. Student's signature:……...................
Field of study. Food Chemistry and Medical Nutrition..Principal Advisor's signature:………
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Contents

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

FOS	fructooligosaccharide
MOM	milk of magnesia
BMI	body mass index
PEG	polyethylene glycol
IBD	inflammatory bowel disease
NEC	necrotizing enterocolitis
°C	degree Celsius
g	gram
mg	milligram
CO_2	carbondioxide
H_2	hydrogen
CH_4	methane
SCFAs	short chain fatty acids
kcal	kilocalorie
kJ	kilojoule
ml	millilitre
ppm	part per million
SD	standard deviation
ND	non-detected
et al.	*et alia* (and others)
e.g.	example

CHAPTER 1

INTRODUCTION

1.1   Background and Rationale

Constipation is a symptom, not a disease or a sign. It is a common problem that occurs in both adults and children. In elderly, this symptom was found about 26% in men and 34% in women (Schaefer and Cheskin, 1998). Approximately 3% of general pediatric outpatients visit and 25% of pediatric gastroenterology consultations are related to a perceived defecation disorder (Fleisher, 1976; Molnar et al., 1983; Taitz et al., 1986). In England, about 5% of children aged 4-11 years had chronic constipation (Yong and Beattie, 1998). In Hong Kong, up to 30% of preschool children in the eastern district had constipation (Ip et al., 2005). In Thailand, there was no data on prevalence of childhood constipation. However, prevalence of constipation in pediatric patients at Queen Sirikit National Institute of Child Health has increased about 0.46-0.55% from 2002 to 2006. The symptoms of constipation include periodic passage of very large amount of stool, hard stool, abdominal pain, nausea, vomiting, flatulence, pain on defecation, blood-streaked stool, and stool frequency less than 3 times per week. Anorexia is often present with constipation (Loening-Baucke, 1993; Croffie and Fitzgerald, 2004).

The causes of constipation vary depending on age. Approximately 90-95% of constipation in children are idiopathic causes (Loening-Baucke, 1993). In a small number of children, constipation may be the results of metabolic causes (hypothyroidism, hypercalcemia, hypokalemia, diabetes mellitus and diabetes insipidus), lead toxicity, Hirschsprung's disease and medication side effects (opiates, phenobarbital, phenytoin, iron supplement and tricyclic antidepressants) (Biggs and

Dery, 2006). However, insufficient intakes of dietary fiber and water, poor bowel habit and withholding their stool for some reasons such as inconvenience to use toilets or emotional stress can induce constipation (Morais et al., 1999; Ip et al., 2005; Lee et al., 2008).

Treatment of constipation is dependent on age and history of children. The treatment program should be designed to clear any existing impaction, prevent reimpaction, and establish a regular bowel habit. There are two phases of treatment. First, they must change their behaviors such as doing more exercise and taking adequate amount of fluids and dietary fiber. The recommended dietary fiber intake in children older than 2 years old is age plus 5 g/day (William, Bollella and Wynder, 1995). Second, medication treatment, which safe for children, is enema therapy (glycerine suppository and normal saline enema) and laxative therapy (mineral oil, magnesium hydroxide, lactulose, polyethylene glycol powder, and sorbitol) (Pashankar and Tolia, 2004). However, defecation trial is very important and must be included in any treatment programs (Loening-Baucke, 1993).

Fructooligosaccharides (FOS) are natural ingredient commonly found in dietary foods. FOS are present as plant storage carbohydrates in a number of vegetables, fruits and plants including wheat, onion, bananas, garlic and chicory (Niness, 1999). FOS are defined as prebiotic because they cannot be digested in gastrointestinal tract. Thus, they beneficially affect the host by selectively stimulating the growth and activity of the species of bacteria in the colon. FOS are not absorbed in the small intestine but are fermented by *Bifidobacterium spp.* in the colon to combustible gases, lactic acid, short-chain fatty acids (SCFAs). SCFA and lactic acid induce low pH in the colon that can inhibit growth of pathogenic bacterias (Walker and Duffy, 1998; Duggan, Gannon and Walker, 2002). The studies about FOS and

inulin supplementations showed that they could induce growth and activity of bifidobacteria in colon, but reduce growth of pathogenic bacterias such as clostridia (bacteria induce diarrhea) (Gibson et al., 1995). Waligora-Dupriet and colleague (2007) found that FOS stimulated bifidobacteria but decreased clostridium growth when compared with the control group. After treatment discontinued for 14 days, the growth of both bifidobacteria and clostridium were not different.

The constipation in adults who received FOS 10 g/day for 30 days improved compared to the control group. They had often defecation and increased weight of feces and SCFA (Chen et al., 2000). Continuous ambulatory peritoneal dialysis patients who received FOS supplementation significantly increased number of defecation (Chaotrakul, 2006). Supplementation of FOS in constipated elderly patients had increased frequency of defecation (Hidaka, Tashiro and Eida, 1991). Side effects of FOS include bloating and flatulence. These symptoms are not severe, and they can be reduced after discontinuing FOS supplementation (Kleessen et al., 1997; Chaotrakul, 2006). However, the study in 2-6 weeks infants who received FOS about 1.5-3 g/day for 7 days, indicated that FOS supplementation stimulated bifidobacteria growth in the colon, increased number of defecations and made stool softer. Safety dose of FOS used in infants (2-6 weeks) is 3 g/day (Euler et al., 2005). Previous study showed that healthy infants (4-12 months) who received 3 g/day of FOS (maximum dose) could tolerate the dose at this level as nausea, vomiting and obstruction in the intestine did not occur in these infants (Moore et al., 2003). Similar results were also found in children aged between 6-24 months who received 2 g/day of FOS. Therefore, FOS supplementation could inhibit growth of pathogenic bacterias, reduce infection in children and did not induce any side effects at this dose.

In many studies, FOS can improve symptoms of chronic constipation in elderly by increasing the number of defecation and stools soften. However, there is no study on the effect of FOS on chronic constipation in children aged between 4-12 year-old. Despite the availability of different laxatives, there are only few studies conducted in children to compare different laxatives with respect to efficacy or safety. Therefore, this study was designed to compare the efficacy, safety and acceptance of FOS versus milk of magnesia, laxatives commonly used in children.

1.2   Objectives of the study

The aim of the study was to determine efficacy (number of defecation, characteristic of stools and symptoms during defecation), safety and acceptance of FOS supplementation with milk of magnesia treatment in children chronic constipation.

1.3   Research variables

Independent variable was a treatment for constipation including FOS and MOM. In addition, advices about dietary pattern and physical activity were also given to the participants

Dependent variable consisted of 4 components: defecation pattern, stool consistency, dietary pattern, and nutritional status.

1.4   Scope of the study

This research was aimed to study in children aged 4-12 years, who visited Outpatient Department of Queen Sirikit National Institute of Child Health.

1.5   Operational definition of terms

Dietary pattern: relation with actual eating habits, its ability to address correlations and interactions among nutrients, and its quantification of the aggregate effect of simultaneous exposure to several dietary factors consumed together.

Defecation pattern: a description of defecation of a person over 4 year-old children such as normal defecation is described by once daily of defecation. If one has less than 3 times/week of defecation, and hard feces, it means constipation or over 3 times/day and watery, it means diarrhea.

Stool consistency: a description of the main stool consistency that was separated into 7 types including separate hard lumps like nut or hard to pass (type 1), sausage-shaped but lumpy (type 2), like a sausage but with cracks on it's surface (type 3), like a sausage or snake, smooth and soft (type 4), soft blobs with clear-cut edges and passed easily (type 5), fluffy pieces with ragged edges or mushy stool (type 6) and watery (type 7).

Nutritional status: the state of person's health in terms of the nutrition in his or her diet. It was separated into normal, underweight, overweight and obesity, which was affected from many factors such as dietary intake and physical activity. Weight gain person may be related with many diseases (diabetes mellitus, hyperlipidemia or hypertension).

CHAPTER 2

LITERATURE REVIEW

2.1 Normal defecation

Stool is normally propelled down the colon to the anorectum where it is stored until it can be eliminated in a socially acceptable manner. The anorectum stores and eliminates stool through a complex mechanism involving muscles of the pelvic floor, the autonomic and somatic nervous system, and the group of muscles controlling the anal sphincters. These interactions have become understood as techniques to study anorectal physiology, such as anorectal manometry, electromyography (EMG), and defecography. The internal and external anal sphincters surrounding the anal canal form an angle (the anorectal angle) with the puborectalis muscle (Figure 1). This angle is approximately 85° to 105° at rest. The bolus of stool is propelled into anorectum during defecation where distention of the wall results in a temporary reflex relaxation of the internal anal sphincters, allowing the stool to come in contact with sensitive receptors in the anal canal. The external sphincter simultaneously contracts, giving the individual time to decide if circumstances are appropriate to allow stool to escape. If the individual decides to allow stool to escape, increased intrarectal pressure from straining moves the fecal material towards the anal canal and the puborectalis muscle relaxes, allowing the pelvic floor to descend. Descent of the pelvic floor straightens the anorectal angle, the external anal sphincter is inhibited, and the fecal material is evacuated. If defecation is to be deferred, voluntary contraction of the puborectalis muscle and the external anal sphincter muscle decreases the anorectal angle to less than the usual 85° to 105°. Then, defecation is prevented, and the rectum accommodates its contents. In newborn babies and very

young infants, the role played by the cerebral cortex in these normal events is not yet developed; therefore, defecation occurs when the internal sphincter relaxes. (Croffie and Fitzgerald, 2004).
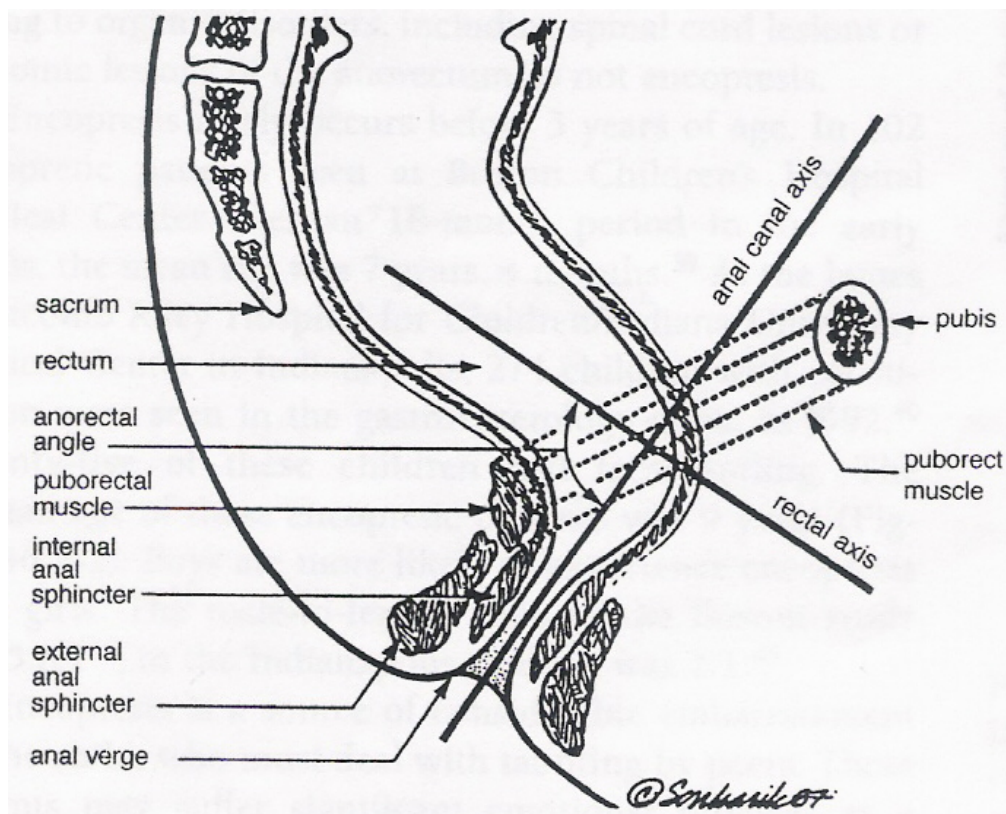
Figure 1 Anatomy of the anorectal region (Croffie and Fitzgerald, 2004)

The normal frequency of bowel movements at different ages has been defined (Table 1). Infants have a mean of four stools per day during the first week of life. This frequency gradually declines to a mean average of 1.7 stools per day at 2 year of age and 1.2 stools per day at 4 years of age (Nyhan, 1952; Weaver and Steiner, 1983). Some normal breast-fed babies do not have stool for several days or longer (Hyams et al., 1995; Baker et al., 1999). After 4 years, the frequency of bowel movements remains unchanged.

Table 1 Normal frequency of bowel movements in infants and children (Fontana et al, 1989)

Age	Mean number of bowel movements per week	Mean number of bowel movements per day
0-3 months: breastfed	5-40	2.9
0-3 months: formula-fed	5-28	2.0
6-12 months	5-28	1.8
1-3 years	4-21	1.4
>3 years	3-14	1.0

2.2 Definition of constipation

Constipation is a symptom, not a disease or a sign. For this reason, a precise definition has been elusive. Constipation has a different meaning for different people and often reflects an individual's view of what the normal pattern of defecation should be. Thus, its definition has included terms such as difficult or infrequent bowel movements, painful defecation, passage of hard stools and a sensation of incomplete evacuation of stool. Chronic constipation is commonly described as constipation of more than 12 weeks duration that dose not respond to dietary fiber or simple therapeutic measures (Bleser et al., 2005). The common criteria used in primarily to clinical research is the Rome III criteria used in diagnosis of constipation (see box below)(Rasquin et al., 2006). Recently, a group of pediatric gastroenterologists and pediatricians meeting in Paris to seek a consensus on terminology for childhood constipation defined chronic constipation as 2 or more of the following occurring over the preceding 8 weeks: frequency of bowel movements less than 3 per week, more than I episode of fecal incontinence per week, large stools

in the rectum or palpable on abdominal examination, passing of stools so large that they obstruct the toilet, retentive posturing and withholding behavior, and painful defecation (Benninga, Candy and Taminiau, 2005).

Rome III Diagnostic criteria for constipation
Must include 2 or more of the following in a child with a developmental age of at least 4 years with insufficient criteria for diagnosis of constipation: 1. Two or fewer defecations in the toilet per week   2. At least 1 episode of fecal incontinence per week   3. History of retentive posturing or excessive volitional stool retention   4. History of painful or hard bowel movements   5. Presence of large fecal mass in the rectum   6. History of large diameter stools that may obstruct the toilet

From Rasquin et al, 2006.

2.3 Epidemiology of constipation

The exact worldwide prevalence of constipation in children is not known. Population-based studies suggest that 10-20% of adults in Western countries and in Asia have one or more symptoms of constipation (Talley et al., 1993; Cheng et al., 2003), and it is estimated that 0.3 to 28% of children worldwide are constipated (Benninga, Voskuijl and Taminiau, 2004). Constipation occurs in all social classes. Contrary to adults where it is much more common in females, childhood constipation probably occurs much more commonly in boys than in girls (Lorenzo, 2001)

Up to one third of children ages 6 to 12 years report constipation during any given year (Felt et al., 2003). Constipation generally first appears between the ages of two and four years (Rubin, 2004).

Encopresis is reported by 35% of girls and 55% of boys who have constipation (McGrath, Mellon and Murphy, 2000). In toddlers (2-4 years old), the distribution of constipation and soiling is equal in boys and girls. However, by school age (five years), encopresis is three time more common in boys than in girls. At the age of 10 years, approximately 1.6% of children still have some encopresis (Abi-Hanna and Lake, 1998).

2.4 Pathogenesis and mechanism of constipation

Difficulties with defecation may result from dysfunction in any portion of normal mechanism of defecation. Such dysfunction may result from aberrations in anatomy or physiology. Constipation is termed idiopathic when it can not be explained by any anatomic, physiologic, radiologic, or histopathologic abnormalities. Although the exact mechanism of idiopathic constipation is not known, it is generally believed that a multiplicity of factors may be involved. The final common pathway is likely to be a decrease in propulsive forces, impaired rectal sensation, or a functional outlet obstruction. A decrease in propulsive forces may result from a genetic predisposition or a structural abnormality of the colon. Abrahamian and Lloyd-Still (1984) obtained a family history of constipation in greater than 40% of 186 constipated children. Concordance for constipation is reported to be six times greater among identical twins than among fraternal twins (Bakwin and Davidson, 1971), and evidence for a congenital syndrome of early-onset constipation has been identified in adults using dermatoglyphics (Gottlieb and Schuster, 1986). Recently, Hubner, Meier-Ruge and Halband (2002) described four patients with severe constipation and abnormal gastrointestinal motility who lacked the connective tissue layer between the circular and longitudinal muscles of the bowel on resected specimers in addition to

having abnormal submucosal ganglia. They referred to these findings as "desmosis of the colon" (Hubner et al., 2002). In addition, Hutson and colleagues (2001) found reduced numbers of excitatory substance P–immunoreactive nerve fibers in circular muscles of laparoscopic colon muscle biopsies obtained from a number of children with slow-transit constipation.

Impaired rectal sensation, whether primary or secondary, may lead to chronic constipation. It is known, for example, that children with spinal cord lesions may develop constipation because of impaired rectal sensation. Meunier, Marechal and de Beaujeu (1979) found that 65 % of 144 children with severe constipation had significant impairment of rectal sensation, which may have been secondary to the megarectum resulting from chronic fecal retention. It could be argued, however, the impaired rectal sensation itself could be the primary event leading to constipation in some children. Functional outlet obstruction leading to constipation may result from spasticity of the levatorani or impaired relaxation of the puborectalis muscle (Read et al., 1986). It is commonly believed that dietary fiber promotes laxation (William et al., 1995). Although there are no randomized controlled studies in children to support this belief, some case-control studies have shown an association between decreased fiber intake and constipation in children (Roma et al., 1999; Guilhon and Calcado, 1999)

Although all of the above mechanisms could lead to chronic constipation, it is believed that most childhood chronic constipations result from intentional or subconscious withholding of stool. Usually, an acute episode precedes the chronic course. The acute episode may occur as the diet is changed from human milk to cow's milk, either because of a higher protein-to-carbohydrate ratio in cow's milk or, possibly, because of allergy to cow's milk protein (Iacono et al., 1998). The stool

which becomes firm and smaller in quantity is passed less frequently and with great effort. Anal irritation and often an anal fissure develop, and defecation becomes painful. If this acute problem is not treated promptly, a pattern of withholding develops as the passage of stool becomes associated with pain (Fitzgerald, 1977). At the urge to pass stool, the infant typically screams, stiffens the body, and tightens the gluteal muscles, while making a great effort to prevent escape of stool. The face might become flushed during this process, and parents often misinterpret these signs as an extreme effort to pass stool.

In toddlers, conflict arising out of coercive or inappropriately early toilet training is an additional factor that may initiate a pattern of stool retention (Christophersen, 1991; Taubman and Buzby, 1997). In older children, a retentive pattern may be initiated by situations that make stooling inconvenient or uncomfortable, such as a school with unpleasant toilet facilities (Barnes and Maddock, 2002) or group A β-streptococcal anusitis (Gleghon, Heyman and Rodolph, 1991; Glayden, 1992). Toddlers and older children tend to cross their legs, stand rigidly upright, squat quietly in corners, walk on or hold onto furniture as they wait for the call to stool to pass. The urge to defecate passes as the rectum accommodates to its content a vicious cycle of retention develops as increasingly larger volumes of stool, desiccated by colonic absorption of the water content, must be expelled, often with increasing difficulty and pain. Prolonged stretching of the rectal walls associated with chronic fecal retention leads to an atonic and desensitized rectum which perpetuates the situation because large volumes of stool must now be present in the rectum to initiate the call to stool. Some of these patients tolerate rectal distention volume in excess of 500 mililiters at anorectal manometry. This functional

megacolon can be demonstrated on a barium enema. It may be confused with the megacolon associated with Hirschspurang disease by the untrained eye.

When large volumes of stool in the rectal vault stretch the rectum, the internal anal sphincter relaxes while the anal canal is shortened, as demonstrated by Loening Baucke and Younoszai (1982). Eventually, the external anal sphincter is no longer able to function adequately when the fecal mass pushes against it. Unformed stool escaping around the impaction leaks uncontrollably into the undergarment. This condition is referred to encopresis (Fitzgerald, 1975).

2.5 Clinical signs and symptoms of chronic constipation

In many children, longer intervals between bowel movements may be the only complaint. Symptoms and signs associated with chronic constipation have shown that stool frequency decreases from 4 or more per day during infancy to about one per day at 4 years of age. Stool frequency of less than 3 times per week at any age is outside the norm (Croffie, 2006). The other symptoms include abdominal pain, anorexia, vomiting, abdominal distention, excessive flatulence, hard stools and blood-streaked stools. Constipation in infants and toddlers may come to parental attention because of increasing irritability, a poor appetite, or withholding behavior. Constipation in most older children comes to attention because of fecal soiling. Initially, the parents assume that the soiling of underclothes is due to reluctance to use the toilet, and they consult a physician only after negative reinforcement has failed. Occasionally, patients referred for chronic diarrhea are found to have retained stool and incontinence on rectal examination (Croffie and Fitzgerald, 2004). However, the assessment of constipation is related to dietary history, amount of fiber and fluid intakes, family and social factors.

2.6 Differential diagnosis

Constipation may be seen in a heterogeneous group of patients. Although no organic cause is identified in most cases, it is important to be able to identify the many conditions whose symptom complex may include chronic constipation (Table 2). The most common condition that must be differentiated from idiopathic constipation is Hirschsprung disease, a colonic motility disorder resulting from segmental colonic aganglionosis, with a prevalence of 1 in 5,000 live births and a male-to-female ratio of 4:1 (Kleinhaus, Boley and Sheran, 1979). It is believed to account for 20 to 25% of all cases of neonatal intestinal obstruction (Fithzgerald, 1977) and 3% of constipated children are referred to the gastroenterologist (Glayden, 1992). It can lead to severe enterocolitis with fever, diarrhea, and severe prostration, which may be fatal if the diagnosis is not recognized early (Bill and Chapman, 1962). Most affected infants develop difficulties with defecation during the first few weeks of life. Other signs and symptoms associated with the condition include abdominal distention, refusal to feed, and bilious vomiting. In the older infant or child in whom the diagnosis is not made earlier in life, may have persistent abdominal distention, recurrent fecal impaction, and failure to thrive. Examination of the rectum in patients with Hirschsprung disease usually reveals an empty vault, although stool is palpable in the abdomen. A gush of air and liquid stool may follow withdrawal of the examining finger. In some patients with short-segment or ultrashort-segment Hirschsprung disease, the diagnosis may not be made until later in life (Udassin, Nissan and Lernau, 1981; Bill and Chapman, 1962). These patients have long histories of chronic constipation and may have ganglion cells on rectal biopsy, despite anorectal manometric findings consistent with Hirschsprung disease. They are

thought to have impaired innervation of some length of the sphincter mechanism (Udassin et al., 1981).

Table 2 Some organic causes of constipation

Causes	Examples
Abnormalities of colon and rectum	Chronic intestinal pseudo-obstruction
	Anal stenosis, ectopic anus
	Anal or colonic stricture-post NEC or IBD
	Postsurgical repair of imperforate anus
Spinal cord lesions	Spina bifida, meningomyelocele
	Sacral agenesis, diastematomyelia
	Spinal cord tumors (lipomas, cysts, teratomas)
Neuropathic lesions of GI	Hirschsprung disease, intestinal neuronal dysplasia
Systemic disorders	Diabetes mellitus, diabetes insipidus
	Hypothyroidism, panhypopituitarism
	Hypocalcemia, hypercalcemia, cerebral palsy
	Dermatomyositis, myotonic dystrophy
	Multiple sclerosis, muliple endocrine neoplasia
	Pheochromocytoma, amyotonia congenital
	Neurofibromatosis, infectious polyneuritis
	Prune-belly syndrome, scleroderma
Drugs	Analgesics, antacids, anticholinergics, bismuth
	Iron, cholestyramine, psychotropics
Others	Celiac disease, cystic fibrosis, lead toxicity

IBD = inflammatory bowel disease; NEC = necrotizing enterocolitis.

2.7 Investigations (Croffie and Fitzgerald, 2004)

Most infants and children with chronic constipation require no laboratory investigation. In a small proportion of these children, clinical evaluation alone is insufficient and/or simple treatment measures are ineffective. In this small group of patients, diagnostic tests such as plain radiographs of the abdomen, barium enema, anorectal manometry, and rectal biopsy may be useful. A urinalysis and urine culture may be indicated in the patient presenting with accompanying complaints such as abdominal pain, enuresis dysuria, urgency, or increased urinary frequency.

Plain radiographs of the abdomen may be necessary to establish a fecal impaction in the child who resists rectal examination and in the obese child when abdominal and rectal examinations are suboptimal. The rectum of the impacted fecal-retentive child is dilated and filled with stool to the anal verge (Figure 2).
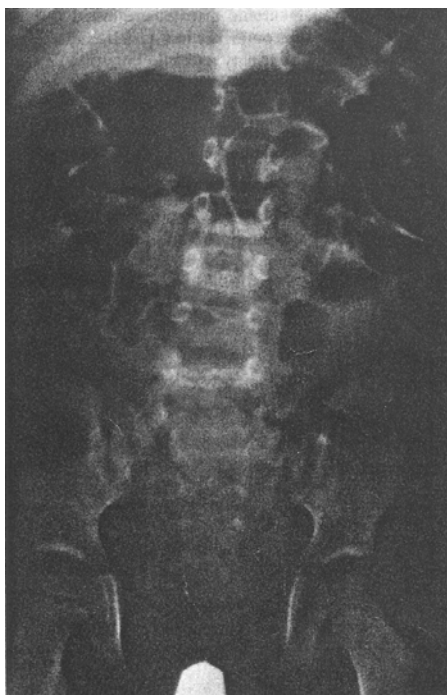
Figure 2 A plain radiograph of abdomen showing a dilated rectum impacted with stool in a child with constipation (Croffie and Fitzgerald, 2004)

The barium enema should be performed on an unprepared colon if the intent is to detect the transition from aganglionic to ganglionic bowel, which is typical of Hirschsprung disease. Usually, the ganglionic segment is dilated with stool, creating a rectosigmoid index (obtained by measuring the maximal diameter of the rectum and comparing it with a similar measurement of the sigmoid colon) of less than 1, with normal being greater than 1. If stool is removed before the barium enema, this transition zone may be difficult to identify, and the rectosigmoid index may be deceptively normal. A transition zone may not be seen in infants simply because there is not enough time to distend the ganglionic portion of the colon with stool. Loening-Baucke and colleagues (1985) calculated the sensitivity and specificity of barium enema in the diagnosis of Hirschsprung disease in the neonate to be 75% and 67% respectively. If the initial barium enema is not diagnostic, 24- and/or 48-hour follow-up plain radiographs of the abdomen, including a direct lateral radiograph of the rectum and sigmoid, may demonstrate delayed excretion of the barium and suggest the diagnosis.

2.8 Management of children with constipation (Baker et al., 1999)

The general approach to the child with functional constipation includes the following steps: determine whether fecal impaction is present, treat the impaction if present, initiate treatment with oral medication, provide parental education and close follow-up, and adjust medications as necessary.

2.8.1 Education

The education of the family and the demystification of constipation, including an explanation of the pathogenesis of constipation, are the first step in treatment. If fecal soiling is present, an important goal for both the child and the

parent is to remove negative attributions. It is especially important for parents to understand that soiling from overflow incontinence is not a willful and defiant maneuver. Parents are encouraged to maintain a consistent, positive, and supportive attitude in all aspects of treatment. It may be necessary to repeat the education and demystification processes several times during treatment (Rappaport and Levine, 1986).

2.8.2   Disimpaction

Fecal impaction is defined as hard mass in the lower abdomen identified during physical examination, a dilated rectum filled with a large amount of stool found during rectal examination, or excessive stool in the colon identified by abdominal radiography (Barr et al., 1979). Disimpaction is necessary before initiation of maintenance therapy. It may be accomplished with either oral or rectal medication. In uncontrolled clinical trials, disimpaction by the oral route, the rectal route, or a combination of the two has been shown to be effective (Tolia, Lin and Elitsur, 1993). There are no randomized studies that compare the effectiveness of one with the other. The oral approach is not invasive and gives a sense of power to the child, but adherence to the treatment regimen may be a problem. The rectal approach is faster but is invasive. The choice of treatment should be determined after discussing the options with the family and child.

Disimpaction with oral medication has been shown to be effective when high doses of mineral oil, polyethyleneglycol electrolyte solutions, or combination is used (Tolia et al.,1993; Gleghorn, Heyman and Rodolph, 1991; Ingebo and Heyman, 1988). Although there are no controlled trials demonstrating the effectiveness of high-dose magnesium hydroxide, magnesium citrate, lactulose, sorbitol, senna, or bisacodyl for initial disimpaction, these laxatives have been used

successfully in that role (Sutphen et al., 1995; Loening-Baucke, 1990). It is recommended that mineral oil, oral electrolyte solution, or the listed laxatives are used alone or in combination for initial disimpaction when the oral route is selected.

Rectal disimpaction may be performed with phosphate soda enemas, saline enemas, or mineral oil enemas followed by a phosphate enema (Nurko et al., 1996; Cox et al., 1994). These enemas are widely used and are effective. The uses of soapsuds, tapwater, and magnesium enemas are not recommended because of their potential toxicities. Rectal disimpaction has also been effectively performed with glycerin suppositories in infants and bisacodyl suppositories in older children (Weisman et al., 1983).

2.8.3   Maintenance therapy

Once the impaction has been removed, the treatment focuses on the prevention of recurrence. In the child who has no impaction or after successful disimpaction, maintenance therapy is begun. This treatment consists of dietary intervention, behavioral modification, and laxatives to assure that bowel movement occurs at normal interval with good evacuation.

Dietary changes are commonly advised, particularly increased intake of fluids and absorbable and nonabsorbable carbohydrates, as a method to soften stools. Carbohydrates and especially sorbitol found in some juices such as prune, pear, and apple juices, can cause increased frequency and water content of stools (Kneepken, 1989; Gryboski, 1966). A balanced diet that includes whole grains, fruits, and vegetables is recommended as part of the treatment for constipation in children.

2.8.4   Behavioral modification

An important component of treatment includes behavior modification and regular toilet habits (Lowery et al., 1985; Howe and Walker, 1992). Unhurried

time on the toilet after meals is recommended. As part of the treatment of constipation, with or without overflow incontinence, it is often helpful to have children and their caregivers keep diaries of stool frequency. This can be combined with a reward system. For example, a child can use a calendar with stickers to record each stool that is passed in the toilet. The calendar can then be taken on visits with the health-care provider and can serve as both a diary and point for positive reinforcement. In cases in which modification or behavioral problems are interfering with successful treatment, referral to a mental health-care provider for behavioral modification or other interventions may be helpful.

The successful treatment of constipation, especially with overflow incontinence, requires a family that is well organized, can complete time-consuming interventions, and is sufficiently patient to endure gradual improvements and replaces. Close follow-up by telephone and by office visit is recommended. Some families may need counseling to help them manage this problem effectively.

2.8.5   Medications

It is often necessary to use medication to help constipated children achieve regular bowel movements (Table 3). A prospective, randomized trial showed that the addition of medications to behavior management in children with constipation is beneficial (Nolan et al., 1991). Children who received medications achieved remission significantly sooner than children who did not. It is possible that the use of laxatives is most advantageous to children until they are able to maintain regular toilet habits.

First treatment of constipation is clear stools in colon (disimpaction) with enemas and then maintenance medication is necessary in the daily treatment. The constipation medications such as mineral oil (a lubricant) or magnesium

hydroxide, lactulose, sorbitol, polyethylene glycol powder (osmotic laxatives), or a combination of lubricant and laxative is recommended. At this stage in the treatment of constipation, the prolonged use of stimulant laxatives is not recommended. Extensive experience with long-term use of mineral oil (McClung, Boyne and Linsheid, 1993), magnesium hydroxide, and lactulose or sorbitol has been reported. Long-term studies show that these therapies are effective and safe (Loening-Baucke, 1993). The doses and potential adverse effects of these medications are found in Table 3. Because mineral oil, magnesium hydroxide, lactulose, and sorbitol seem to be equally efficacious, the choice among these medications is based on safety, cost, the child's preference, easy of administration, and the practitioner's experience but there are few studies compared oral medications for children constipation. One study found that the osmotic laxative, polyethylene glycol (PEG 3350), was significantly more effective and safer than lactulose during 8 weeks treatment period (Voskuijl et al., 2004). Randomized trial has found that PEG 3350 and magnesium hydroxide were equally effective in long-term treatment. PEG 3350 was safe for long-term treatment and was better accepted by children than magnesium hydroxide (Loening-Baucke and Pashankar, 2006). In addition, the stimulant laxatives may be necessary intermittently, for short periods, to avoid recurrence of an impaction (Nurko et al., 1996). In this situation the use of stimulant laxatives is sometimes termed rescue therapy.

Table 3 Medications for constipated children 1 year old or more

Laxatives	Dosage	Side effects
Rectal administration		
Enemas:	6 ml/kg (maximum dose:	Risk of mechanical trauma to rectal
- normal saline	135 ml)	wall, abdominal cramping or
		vomiting.
Glycerine suppository	-	No side effects
Bisacodyl suppository	One-half to one suppository	Abdominal cramping, diarrhea and
(10 mg)	administered once or twice	hypokalemia, abnormal rectal
	daily	mucosa and (rarely) proctitis
Oral administration		
Lubricant	1-3 ml/kg per day given	Risk lipoid pneumonia if aspirated
- mineral oil (soften stool)	once daily or divided doses	
	twice daily	
Osmotic laxative	1-3 ml/kg per day in divided	Flatulence, abdominal cramps,
- Lactulose	dose twice daily	hypernatremia (high dosage)
- Magnesium hydroxide	1-3 ml/kg per day in divided	Infants are susceptible to magnesium
(milk of magnesia,	doses twice daily	poisoning. Over dose can lead to
MOM)		hypermagnesemia,
		hypophosphatemia and secondary
		hypocalcemia
Osmotic laxative	1 g/kg per day in divided	Titrate dosage at three-day intervals
- Polyethylene glycol	doses twice daily	to achieve mushy stool consistency
(PEG 3350)		
- Sorbitol	1-3 ml/kg per day in divided	Same as lactulose
	dose twice daily	
Stimulants	1-3 tablets given once or	Abdominal cramping, diarrhea and
- Bisacodyl 5 mg/tab	twice daily	hypokalemia

From Biggs and Dery, 2006.

Maintenance therapy may be necessary for a long time (several months) when the child has been having regular bowel movements without difficulty. Discontinuation of maintenance therapy is considered. Primary care providers and families should be aware that relapses are common and the difficulty of bowel movements may continue though adolescence. Long-term follow-up studies have demonstrated that a significant number of children continue to require therapy to maintain regular bowel movements (Staiano et al., 1994; Loening-Baucke, 1993).

However, nondigestible carbohydrates have a laxative effect on bowel habit. The mechanism works via stimulation of microbial growth, increase in bacterial cell mass, and stimulation of peristalsis by the increased bowel content (Cummings, Macfarlane and Englyst, 2001). So use of prebiotics or dietary fibers is an alternative choice for treatment of constipation in children.

2.9 Fructooligosaccharides (FOS)

Synonym of fructooligosaccharide is oligofructose containing 2-10 monosaccharide residues connected by glycosidic linkages (IUB-IUPAC Joint Commission on Biochemical Nomenclature, 1982). They are widely distributed in plants and vegetables, including banana, plum, onion, shallot, asparagus, chicory and artichoke (Campbell et al., 1997; Hogarth et al., 2000) but content of FOS in each food is different (Table 4) (Moshfegh et al., 1999).

2.9.1   <u>Characteristics of fructooligosaccharides</u> (Figure 3)

FOS has been defined as a combination of the three sugars such as:

- 1-kestose (β-D-Fru-$(2\rightarrow1)_2$-α-D-glucopyranoside, GF2)

- nystose (β-D-Fru-$(2\rightarrow1)_3$-α-D-glucopyranoside, GF3)

- fructofuranosylnystose (β-D-Fru-(2→1)$_4$-α-D-glucopyranoside, GF4)

Fructosyl unit (F) are bound at the β (2→1) position of sucrose (GF) and using fructosyl-transferase (β-fructofranosidase), which can transfer a fructosyl group of sucrose to the terminal fructose of accepter (Lewis 1993; Yun 1996; L'homme, Puigserver and Blagini, 2002; Franck 2002; Hirayama 2002). FOS is white powder, soluble in water and has a taste profile similar to sucrose, without its cooling effect. When purified, the sweetness is 30% of that of sucrose. Water-retention capacity is higher than that of sucrose, similar to sorbitol. Being nonreducing sugars, FOS do not result in the Maillard reaction. They are stable at pH >3 and temperatures up to 140 ^{o}C (Bornet, 1994; Franck, 2002).

2.9.2   Production of fructooligosaccharides

2.9.2.1 Synthesis from sucrose

FOS are synthesized from sucrose by repeated fructosyl transfer from a fructosyl donor which have a terminal glucose unit. The enzyme generally considered to be involved in plant fructan synthesis is sucrose-sucrose fructosyl transferase or β-fructofranosidase (from *Aspergillus niger*), which catalyses the transfer of a fructose molecule from one sucrose molecule to another, leading to kestose (glucosyl-1, 2 fructosyl-1,2 fructose), nystose and fructofuranosylnystose, respectively (Kaur and Gupta, 2002; Hirayama, 2002).

2.9.2.2 Synthesis from inulin

The production process of FOS represented in Figure 4 involves the extraction of the naturally occurring inulin from chicory roots, in a manner very similar to extraction of sucrose from sugar beets (diffusion in hot water), hydrolysis by endo-inulinase and refine using technologies from the sugar and starch

industries (e.g. ion exchangers), and then evaporation and spray-drying (Franck, 2002).

Table 4 Fructooligosaccharide content in some foods

Foods	Fructooligosaccharide (gram/100 grams)	
	Range	**Midpoint**
Banana		
Raw	0.3-0.7	0.5
Raw-dried	0.9-2.0	1.5
Canned	0.1-0.3	0.2
Asparagus		
Raw	2.0-3.0	2.5
Boiled	1.4-2.0	1.7
Chicory root	19.6-26.2	22.9
Garlic		
Raw	3.6-6.4	5.0
Dried[1]	8.1-14.5	11.3
Globe artichoke	0.2-0.7	0.4
Jerusalem artichoke	12.0-15.0	13.5
Onions		
Raw	1.1-7.5	4.3
Raw-dried	4.7-31.9	18.3
Cooked	0.8-5.3	3.0
Wheat		
Bran-raw	1.0-4.0	2.5
Flour-baked	1.0-3.8	2.4
Flour-boiled	0.2-0.6	0.4

Source : Moshfegh et al, 1999; [1] Calculated using a total solids approach.
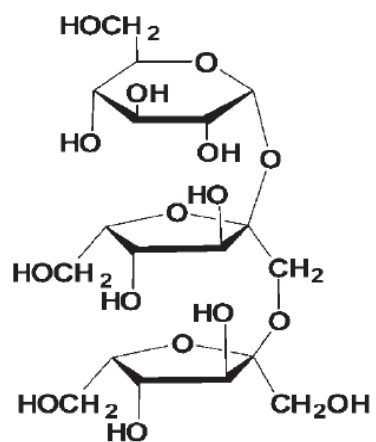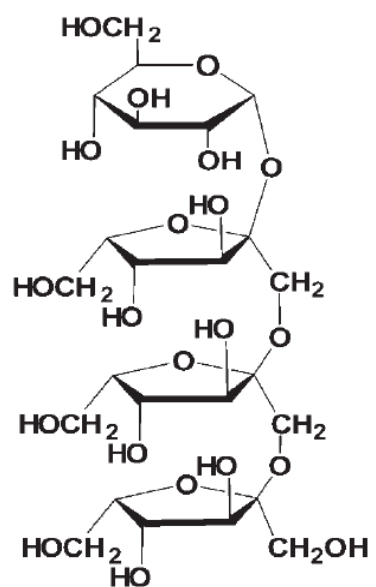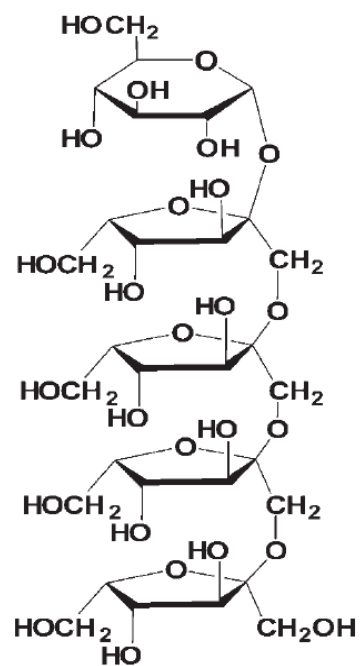
Figure 3 Chemical structure of fructooligosaccharide

While   G = terminal glucosyl unit

                 F = fructosyl units

                 n = the number of fructosyl umits

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                    ┌─────────────────────┐
                    │    Chicory roots    │
                    └──────────┬──────────┘
                               │
                               ▼
                    ┌─────────────────────┐
                    │ Hot water extraction│
                    └──────────┬──────────┘
                               │
                               ▼
                    ┌─────────────────────┐
                    │  Ezymatic hydrolysis│
                    └──────────┬──────────┘
                               │
                               ▼
                    ┌─────────────────────┐
                    │    Purification     │
                    └──────────┬──────────┘
                               │
                               ▼
                    ┌─────────────────────┐
              ┌─────┤    Evaporation      ├─────┐
              │     └─────────────────────┘     │
              ▼                                 ▼
┌─────────────────────────────┐       ┌──────────────┐
│ Fructooligosaccharide syrup │       │ Spray-drying │
└─────────────────────────────┘       └──────┬───────┘
                                              │
                                              ▼
                              ┌───────────────────────────────┐
                              │ Fructooligosaccharide powder  │
                              └───────────────────────────────┘
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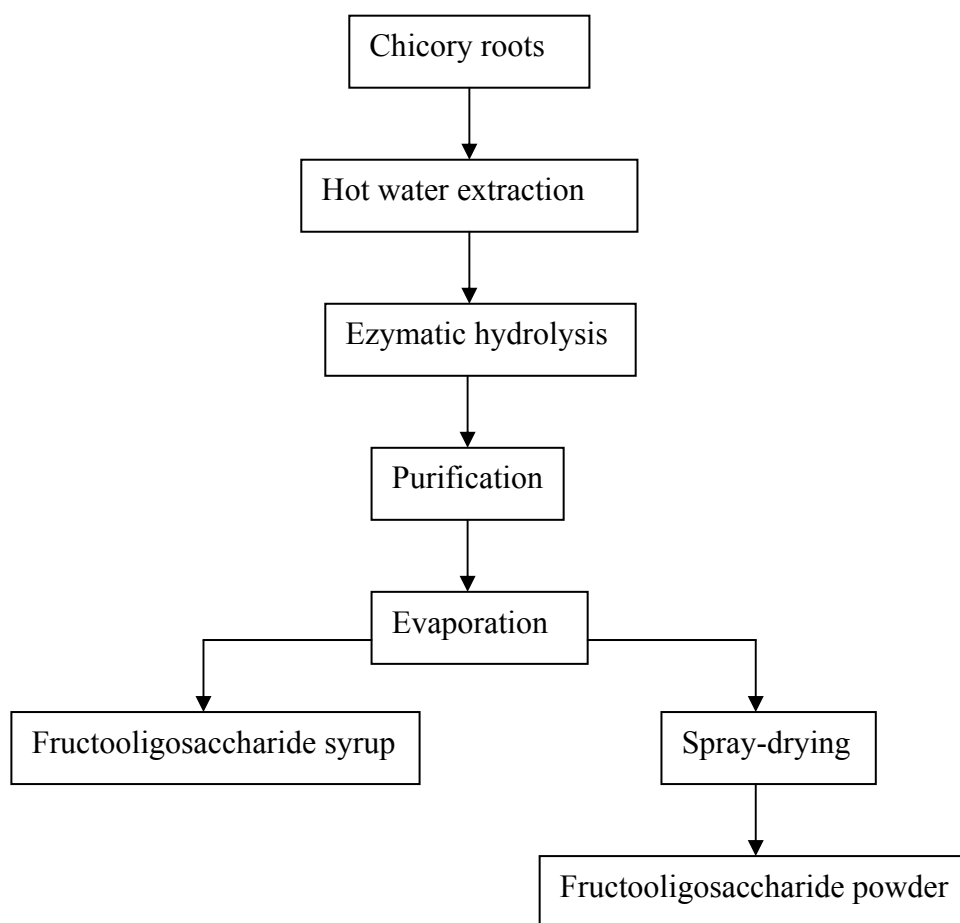
Figure 4 Industrial production process of chicory fructooligosaccharides

2.9.3   Physiological properties of fructooligosaccharides (Kaur and Gupta, 2002)

2.9.3.1 *Prebiotics*

Food ingredient classified as prebiotic has specific properties including neither be hydrolyzed nor absorbed in upper part of the gastrointestinal tract, selective substrate for one or limited number of potentially beneficial commensal bacteria in colon, thus stimulating the bacteria to grow, become metabolically activated, and alter the colonic microflora towards a more healthier composition (Collin and Gibson, 1999).

FOS are prebiotic, nondigestible carbohydrates which are completely fermented in colon, that beneficially affect the host by selectively stimulating the growth and activity of one species or limited number of bacteria species already resident in the colon (Gibson and Roberfroid, 1995). In addition, a prebiotic may repress the growth of pathogens for over all beneficial health because of decrease luminal pH and create an environment less favorable for pathogenic species (Roberfroid, 2001; Topping and Clifton, 2001). Because of the β-configuration of the anomeric C_2 in their fructose monomers, FOS are resistant to hydrolysis by human digestive enzymes (α-glucosidase, maltase, isomaltase, sucrose) which are specific for α-glycosidic bonds, and are thus classified as non-digestible oligosaccharide on the basis of both *in vitro* and *in vivo* data. Since the stomach hydrolysis of FOS is of limited physiological significance, these products pass undigested through the upper part of the gastrointestinal tract into the colon. The passage through the small intestine could be due to fermentation by the microbial population colonizing the ileum. Production of fermented carbohydrates by colonic microflora is gas (CO_2, H_2 and CH_4) and organic acids, among which lactic acid and short-chain fatty acids (SCFAs) are found in colonic contents. The major parts of SCFAs are absorbed and only a small, unrepresentative fraction is found in stools. SCFAs including acetate, propionate and butyrate are important anions in the colonic lumen, affecting both colonocyte morphology and function. By stimulating sodium and fluid absorptions and exert proliferative effects on the colonocyte. SCFAs may enhance colonic blood flow and enhances ileal motility (Scheppach, 1994). SCFAs are used as an energy substrates of colonic epithelium and appear to promote the health of the intestinal mucosa (Velazquez et al., 1997; Cherbut, 2002).

2.9.3.2 *Effect of fructooligosaccharides on the growth of bifidobacteria*

Bifidobacteria are reasonable target organisms for prebiotics and beneficial bacteria in human gut. Advantages of bifidobacteria proliferation in the human large gut include inhibition of pathogen growth, immunomodulating activity, restoration of gut flora after antibiotic therapy, production of digestive enzymes, positives effect on antibiotic-associated diarrhea and repress of rotavirus (Collin and Gibson, 1999), production of vitamin B group and folic acid, and reduction of blood ammonia level (Kaur and Gupta, 2002). Many studies confirm that FOS have a bifidogenic effect. *In vitro* studies about the effect of FOS in minimum levels, it could induce growth stimulation of bifidobacteria even at dose 1 g/day (Reading et al., 1998). Wang and Gibson (1993) showed that FOS induced significant increases in the number of bifidobacteria. Other studies in human also showed that FOS stimulated the growth of bifidobacteria and enterobacteria (Roberfroid, 1997; Bouhnik et al., 1999; Rao, 1999; Bruggencate, Bovee-Oudenhoven and Lettink-Wissink, 2003; Bouhnik et al., 2004).

2.9.3.3 *Effect of fructooligosaccharides on mineral absorption*

Some studies suggest that prebiotics improve calcium absorption from the human colon (Coudray et al., 1997; Heuvel et al., 1999). However, some studies showed that FOS did not interfere about mineral absorptions. No definitive clinical studies support the animal studies to suggest that other minerals (magnesium, iron and zinc) are similar affected (Duggan, Gannon and Walker., 2002). Mechanisms by which ingestion of FOS improves mineral absorption is not very clear (Kaur and Gupta, 2002).

2.9.3.4 *Effect of fructooligosaccharides on lipid metabolism*

There are some evidences suggesting that FOS, especially product of fermentation is propionic acid, may also inhibit the esterification step of fatty acids into triacylglycerols. This is relatively modest in comparison with the marked inhibition of fatty acid synthetase which characterizes the response to FOS in animal. Nevertheless, inhibition at this step could conceivably be responsible for some of the observed effects in humans particularly in subjects with hyperlipidemia where fatty acid esterification rates may be high (Williams and Jackson, 2002). However, no effect of FOS on HDL cholesterol and serum triglyceride concentrations (Williams, 1999) (Figure 5).

2.9.4   Caloric value of fructooligosaccharides

Caloric value of FOS is estimated to be 1.5 kcal/g (6.3 kJ/g) or 38% of a digested hexose molecule. Because FOS resist digestion in the upper part of gastrointestinal tract but can be quantitatively hydrolyzed and fermented by the bacteria in the colon. Consequently, in term of caloric value, FOS do not behave like digestible carbohydrate which has been assigned a caloric value of 3.9 kcal/g (16.3 kJ/g) (Roberfroid, 1999).

2.9.5   Evaluation of safety of fructooligosaccharides

(Carabin and Flamm, 1999)

2.9.5.1 Acute toxicity

Acute toxicity in mice and rats exposed to dietary FOS. The groups were administered 0, 3, 6 and 9 g/kg FOS by gavage. The concentrations were adjusted so that the total volume of solution given per animal was 0.5 ml for mice and 2 ml for rats. Following a single oral dose the animals were observed for any signs of toxicity until the seventh day. No abnormalities were seen in the general state of

health of male and female mice and rats. There were no deaths and increase in body
weight after 7 days, was the same as that in the controls.

Fructooligosaccharides (FOS)

Fermentable by Bifidobacteria

Short chain fatty acids (SCFAs)

Cholesterol

Acetate   **Propionate**   **Butyrate**

Mevalonic acid

Methyl malonyl CoA

HMGCoA reductase

Succinyl CoA

β Hydroxy β-methyl glutaryl CoA

Pyruvatecarboxylase

Pyruvate ⟶ **Phosphoenol pyruvate**
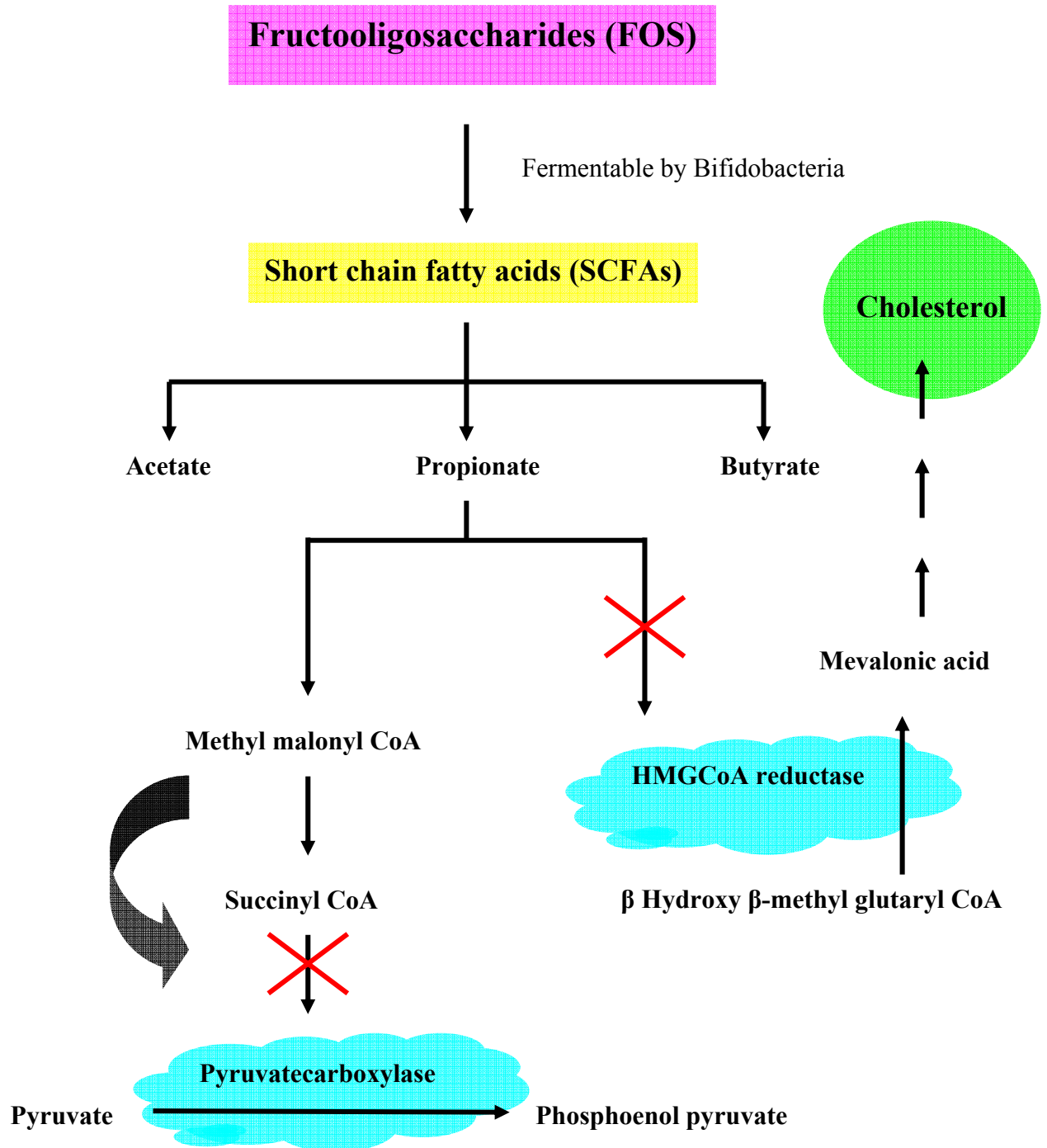
Figure 5 Inhibition of pyruvate carboxylase by methyl malonyl CoA, and HMG CoA

reductase by propionate

2.9.5.2 Subacute toxicity

Male rats, 6-7 weeks old, were used in groups of 18. FOS were used as test substances, while sucrose and glucose were the control subtances. Test and control substances were given daily by gavage at dose of 1.5, 3 and 4.5 g/kg for 6 weeks. On the second, fourth, and sixth weeks, blood samples were obtained from 6 animals in each group. Results revealed that there were no abnormalities or deaths during the study. A slight increase in body weight was observed in the 3 and 4.5 g/kg groups compared to the controls. The other group showed the same trend as the control.

2.9.5.3 Chronic studies

The test in rats, 50 males and 50 females, began receiving FOS for 104 weeks with their diet at concentrations of 0, 8,000, 20,000 and 50,000 ppm (equivalent to 341, 854 and 2,170 mg/kg/day in male rats and 419, 1,045 and 2,664 mg/kg/day in female rats). All animals were observed twice daily and body weights were determined weekly in the first 26 weeks and biweekly thereafter. Results indicated that survival of both sexes, in all test groups, was unrelated to treatment. Body weight gain, food intake, and organ weight for both sexes were unaffected by FOS supplementation. Male rats in the 20,000-ppm FOS group had slightly elevated levels of blood glucose and creatinine. The males in the 50,000-ppm group showed a decrease in creatinine levels. All other parameters in the male and female treated groups were similar to those in the controlled group but in female rats have slight elevation of uric acid in the 8,000- and 20,000-ppm groups.

2.9.5.4 Side effect of fructooligosaccharides

The side effects generally present as GI symptoms such as flatulence, bloating, abdominal distention, borborygmi and rumbling. Furthermore,

through animal studies it has been documented that FOS induce less diarrhea than maltitol and significantly less than sorbitol. Cause of side effects is malabsorption of carbohydrates in the upper GI tract and fermented by colonic flora in colon and then result in production of gas.

2.9.6 Application of fructooligosaccharides in food industry

FOS are commonly used in cereals, fruit preparations for yogurt, frozen desserts, cookies, and nutritional daily products (Niness, 1999; Franck, 1999). FOS, fiber ingredient, often lead to improve taste and texture in bakery products and breakfast cereals (Frank and Coussement, 1997). FOS give more crispness and expansion to extruded snacks and cereals, and also increase shelf life such as keeping breads and cakes moist and fresh for longer. The solubility allows fiber incorporation in watery systems such as drinks, dairy products and table spreads. On the other hand, FOS are more and more applied in functional foods, especially in whole range of dairy products, as prebiotic ingredients which stimulate the growth of beneficial intestinal bacteria (Coussement, 1996; Walter, 1999; Frank, 2002). The incorporation of FOS (1-3%) in the recipe, often through the fruit preparation, improves mouthfeel, reduce syneresis and offers a synergistic taste effect in combination with aspartame and acesulfame K, without significantly increasing the caloric content.

2.9.7 Legal status of fructooligosaccharides (Coussement, 1999)

FOS are legally classified as food or food ingredients, and not as additives, in all countries in which it is used. Although this seems evident if one considers the nutrition properties and the use of both substances, it has not been easy to obtain confirmation of this legal status from many of the legal authorities in the world. The European Union Standing Committee meeting of confirmed that FOS are a food ingredients and accepted use without limitations.

2.10 Fructooligosaccharides and constipation

Non-digestible carbohydrates or fiber-containing products have a laxative effect on bowel habit. The mechanism is stimulation of microbial growth, increase in bacteria cell mass, and thus, stimulation of peristalsis by the increased bowel content, therefore, colonic motility is increased (Roberfroid 1993; Cumming et al., 2001) because of they can contribute directly to increased fecal bulk and the mass of the water they attract (Flamm et al., 2001).

The study of Gibson et al. (1995) was designed to determine effects on the large bowel microflora and colonic function. Eight subjects participated in the study during which they ate controlled diets and received FOS 15 g/day for 15 days. Results showed that FOS increased stool output significantly from 136 to 154 g/day and significantly increased bifidobacteria from 8.8 to 9.5 $\log_{10}$ g/stool, whereas bacteroides, clostridia, and fusobacteria decreased when the subjects were fed with FOS.

Chen et al. (2000) studied in five chronic constipated elderly subjects receiving 2 consecutive periods: a 30 days control period followed by a 30 days experiment period in which FOS was supplemented 10 g/day. Results indicated that FOS increased stool output significantly from 32.4 to 69 g/day and significantly increased frequency of defecation and concentration of SCFAs in stools. No effect on serum glucose, total protein and albumin concentrations of the subjects in the study.

Euler et al. (2005) studied in health term infants (2-6 weeks old). They received human milk or normal formula or addition with FOS 1.5 or 3 g/day for 7 days. During the study, the stools were collected with recorded consistency, culture for bifidobacteria was performed, and adverse events of FOS were observed. After 7 days of both concentration FOS supplementations the bifidobacteria count in the

intervention group were greater than that in the normal formula group. FOS (3 g/day) supplementation resulted in more frequent and significantly softer stools. Adverse event occurred during supplementation with FOS were flatulence, loose stools, emesis, and decreased appetite. However, the similar results were obtained in infants with an FOS supplemented cereal (0.75 and 3 g/day) for 28 days (Moore et al, 2003). It was reported that FOS could increase number of stools per day and lead to more regular and softer stools without diarrhea and be well tolerated in doses of up to 3 g/day.

Bettler and Euler (2006) studied in health term infants ($\leq$ 14 days) about evaluation of growth. They were randomly assigned to 1 of 3 formulas (bovine milk-based control formula or experimental formulas supplemented with FOS either 1.5 or 3 g/day for 12 weeks. They were assessed about anthropometric measurement at baseline, 4, 8 and 12 weeks. Adverse events and tolerance were observed at baseline and 12 weeks. Results indicated that all 3 formulas were judged to be safe and support normal growth but one formula which had significantly less constipation was formula with addition FOS 3 g/day. While both of formulas supplemented with FOS 1.5 or 3 g/day had flatulence more than the control formula. There were not differences in incidences of diarrhea, loose stools, dehydration or allergic reaction among the three groups.

In vivo study, Juskiewicz et al. (2007), studied the effect of supplementation with probiotic and FOS in cecum of Wistar rats. The basal diet (without or with the probiotic preparation) was combined with 2% or 5% FOS for 4 weeks. After discontinued, they were assessed about the content of ammonia, SCFAs and protein concentrations. Results indicated that the group which was administered with 5% FOS had significantly increased on the weight of the cecal digesta, whereas both

levels of the FOS preparation increased the cecal tissue mass compared with the other formulas. The increase in weight of cecal digesta was caused by increased bacteria proliferation and by the capacity of those carbohydrates to hold water in the cecum. The lowest ammonia, highest protein and highest SCFA concentrations were found in the formula with addition 5% FOS. So, this study had concluded that formula with supplemented FOS could be beneficial for gut more than the other, whereas the probiotic supplementation did not affect the cecal metabolism in rat.

CHAPTER 3

MATERIALS AND METHODS

This chapter describes the clinical trial in pediatric constipation which determined the efficacy of fructooligosaccharide (FOS) treatment compared with milk of magnesia (MOM) at Queen Sirikit National Institute of Child Health.

3.1 Clinical trial

3.1.1 Research design

This research was a prospective, parallel group study comparing the efficacy, safety and acceptance between the interventions of FOS and MOM.

3.1.2 Subjects

. All new pediatric patients who were referred to the Pediatric Gastroenterology Outpatient Clinic at Queen Sirikit National Institute of Child Health for treatment of chronic constipation from September 2007 to March 2008 were eligible for the study. The subjects were recruited by pediatric gastroenterology physicians with the following inclusion criteria:

- o Children aged 4-12 years

- o Presence of constipation for more than 3 months with or without fecal incontinence

- o Constipation was defined based on 2 or more of the following characteristics (the Rome III criteria):

  - ▪ Frequency of bowel movement: less than 3 stools per week

  - ▪ More than 1 episode of fecal incontinence per week

  - ▪ Large stools noted in the rectum or felt during abdominal

examination

- Passing of large stools so that obstructed the toilet

- Retentive posturing (withholding behavior)

o Not receive medicines which induce constipation such as: antidepressants, antacid, ferrous sulfate supplement, and cholestyramine

o No treatment with any laxatives 2 weeks before participating in this study

o No diseases or conditions including:

- Chronic intestinal pseudo-obstruction

- Hirschsprung's disease

- Previous surgery involving the colon or anus

- Thyroid function disorder

- Seizure

- Diseases related to gastrointestinal tract, liver, pancreas and spleen

The study protocol was approved by the Institute Ethics Committee of the Queen Sirikit National Institute of Child Health, Bangkok. The subjects older than 7 years of age gave written assent and all their parents gave written informed consent.

The number of patients enrolled in this study was calculated as followed:

$$n = \frac{NZ^2pq}{Nq^2 + Z^2pq}$$

While   n   =   number of sample

N = number of 4-12 years old pediatric constipation patient at Queen Sirikit National Institute of Child Health (196)

Z = 1.96 (α = 0.05)

p = proportion of pediatric constipation from Hidaka et al (1991) were 0.9

q = 1-p

The number of pediatric patient in this study was

$$n = \frac{194(1.96)^2(0.9)(0.1)}{194(0.1)^2 + (1.96)^2(0.9)(0.1)}$$

$$= 29.34 \approx 30$$

3.1.3 Research instruments

3.1.3.1 Materials

- Fructooligosaccharide powder (Helm Mahaboon Company) was formulated to FOS preparation (Appendix D)

- Milk of magnesia suspension (GPO)

3.1.3.2 Tools for nutritional assessment

- Weight and Height Scaling Apparatus which has 0.1 kilogram scale of weight and 0.1 centimeter scale of height

- The growth chart of the Pediatric Endocrine Society of Thailand for children aged 2-19 years old referred from National Growth References for children under 20 years of age from Nutrition Division, Department of Health, Ministry of Public Health. Thailand, 1999 (Appendix B).

3.1.3.4 Documents

- Patient record form (Appendix B)

  Part 1 History of patients

Part 2 Daily of activity, exercise and consumption

Part 3 Weight and height record

Part 4 History of defecation in last 3 months.

- The defecation and side effect record form (Appendix B)

- The information sheet and consent form for participants
  (Appendix C)

3.1.4   Research procedure (Figure 6)

3.1.4.1 Before the intervention, the subjects were assessed and interviewed by the physician and researcher.

1) Data about demographic characteristics and the pattern of defecation were investigated. The pattern of defecation included age at the time of development of constipation, presence of retentive behavior, frequency of defecation per week, size, and consistency of stools defecated into toilet, presence of abdominal pain, urinary incontinence during defecation, presence of blood in stool, one's daily tasks, stooling habits, and fecal incontinence (Appendix B).

2) The nutritional status of the subjects was assessed. The assessment included weight for height, weight for age, height for age, and body mass index (BMI). These parameters were determined as percentiles on the reference growth Chart (Pediatric Endocrine Society of Thailand for children 2-19 years old) (Appendix B).

3) Dietary intake pattern of the subjects was estimated by 24-hour recall (Appendix B).

3.1.4.2 During treatment, all subjects and their parents were aware of the study group assignment. The subjects were divided into 2 groups. Each group received initially either 5 g/day (30 mL/day) of FOS or 1.2-2.4 g/day (15-30 mL/day)

of MOM at bedtime daily (not more than 30 mL/day) for 6 weeks. All of them returned to the clinic two times (2 and 6 weeks after treatments). Each visit the subjects were assessed about nutritional status, pattern of defecation (stool consistency, defecation per week, symptoms during defecation), and adverse effects of the study laxatives (Appendix B). In addition, the subject's compliance was evaluated by counting the amount of returned laxatives, and the assessment on food intake was performed by three-day food records (2 weekdays and 1 weekend day) at week 6 (Appendix B). However, the laxative dosage was adjusted if necessary throughout the study. A normal saline enema was given when the subject was impacted. The subjects who did not return for a planned follow-up visit were monitored the follow-up data through a telephone call.

3.1.5 Outcome of defecation

Constipation improvement was defined as ≥ 3 bowel movements per week, no abdominal pain, no presence anus pain (Loening-Baucke and Pashankar 2006), and improvement of stool consistency. The stool consistency was interpreted using the Bristol Stool Form Scale (Candy and Edwards, 2003). If the stool consistency was defined type 4, it meant improvement of constipation (scale calculated stool consistency type 4 were 4). The example of stool record and form to fill were given to each subject (Appendix B).

3.2 Statistical analysis

Efficacy analyses were performed as improvement of constipation Comparisons were made between the initial data and the follow-up data within and between groups. Statistical analyses included means and standard deviation, Independent t-test, ANOVA and Chi-Square test, with significant level at 5%.

Group 1: FOS 5 g/day for 6 weeks

Group 2: MOM 1.2-2.4 g/day for 6 weeks

2 weeks 4 weeks

Day 0 Day 14 Day 35 Day 42

Weight and height measurements

Dietary record (24-hour recall)

Pattern of defecation

Questionnaires

Nutrition advice

Weight and height measurements

- Weight and height measurements
- Pattern defecation
- Dietary record (3-day record) at week 6

Frequency of defecation record
Stool consistency record
Adverse effect record

Figure 6 Diagram of research procedure

CHAPTER 4

RESULTS

The present research was conducted to study the efficiency of FOS in constipated pediatric patients and the results were compared with MOM, first choice of treatment in pediatric patient at Queen Sirikit National Institute of Child Health. The frequency of defecation per week, characteristic of feces (stool consistency) and side effects of each treatment were observed. Dietary intakes were assessed by 24-hour recall (before treatment) and 3-day food record (after treatment).

4.1   Characteristics of the subjects

There were 63 patients enrolled in this study (38 males and 23 females). Patients were randomly allocated to receive either FOS or MOM and were assigned to one of the two groups. The FOS group comprised of 27 patients (17 males and 10 females) and the MOM group comprised of 36 patients (23 males and 13 females). Nine patients did not complete the study because 5 patients lost follow-up (1 in the FOS group and 4 in the MOM group) and 4 patients did not continue the treatment (1 in the FOS group and 3 in the MOM group). Therefore, there were totally 54 subjects participating in the study throughout 6 weeks [34 males (62.96%) and 20 females (37.04%)]. The characteristics of the subjects are presented in Table 5. The FOS group included 25 subjects (16 males and 9 females) and the MOM group included 29 subjects (18 males and 11 females). Average age of the FOS and MOM groups were 6.68 ± 2.5 and 6.21± 2.37 years respectively. Almost all of them were in normal range of growth (94.4%) and 5.6% were slightly overweight. Most of them were preschool children (51.9%). Approximately 90% of the subjects consumed vegetables 1-2

times/week and drank water less than 4 glasses per day. Most of them often consumed carbonated beverages, soft drinks, fruit juices, and snacks. Most subjects (83.3%) had no exercise. Most of them spent time in watching television, playing computer and reading cartoon books (Table 6)

Following the inclusion criteria, all subjects had defecation less than 3 times per week. Most of them had feces as separated hard lumps, like nut (98.2%), get strain (83.3%) and had painful during defecation every time (72.2%). In addition, they had stomachache during defecation and blood-streaked stool were found in most subject (74.1% and 57.4% respectively). All of them had painful at anus.

Table 5 The characteristics of the subjects.

Characteristics	FOS group number (%)	MOM group number (%)	Total number (%)
Sex			
Males	16 (64.0)	18 (62.1)	34 (63.0)
Females	9 (36.0)	11 (37.9)	20 (37.0)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 0.021$	df = 1	$p = 0.884$
Age (months)			
48-83	14 (56.0)	19 (65.5)	33 (61.1)
84-119	6 (24.0)	7 (24.2)	13 (24.1)
120-155	5 (20.0)	3 (10.3)	8 (14.8)
Total	25 (100.0)	29 (100.0)	54 (100.0)
Mean of age (years)	6.68 ± 2.5	6.21 ± 2.37	
	$\chi^2 = 5.646$	df = 8	$p = 0.687$
	t = 0.714	df = 52	$p = 0.755$
Nutritional status			
Normal	24 (96.0)	27 (93.1)	51 (94.4)
Overweight	1 (4.0)	2 (6.9)	3 (5.6)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 0.215$	df = 1	$p = 0.643$
Degree of education			
Not attend school	3 (12.0)	0 (0.0)	3 (5.6)
Preschool	11 (44.0)	17 (58.6)	28 (51.9)
Grade 1-3	6 (24.0)	7 (24.2)	13 (24.1)
Grade 4-6	5 (20.0)	5 (17.2)	10 (18.4)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 4.089$	df = 3	$p = 0.252$
Illness			
None	21 (84.0)	22 (75.9)	43 (79.6)
Allergy	3 (12.0)	5 (17.2)	8 (14.8)
Others	1 (4.0)	2 (6.9)	3 (5.6)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 0.563$	df = 2	$p = 0.755$

Table 6 Dietary pattern and physical activity of the subjects before treatment

Characteristics	FOS group	MOM group	Total
	number (%)	number (%)	number (%)
Frequency of vegetable intake (times/week)			
1-2	21 (84.0)	28 (96.5)	49 (90.7)
3-4	4 (16.0)	1 (3.5)	5 (9.3)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 2.518$	df = 1	$p = 0.113$
Proportion of high-fiber food intake per day			
None	21 (84.0)	28 (96.5)	49 (90.7)
< One half of whole meal	4 (16.0)	1 (3.5)	5 (9.3)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 2.518$	df = 1	$p = 0.113$
Amount of water intake per day			
< 1000 mL (< 4 glasses)	21 (84.0)	28 (96.5)	49 (90.7)
> 1000 mL (> 4 glasses)	4 (16.0)	1 (3.5)	5 (9.3)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 2.518$	df = 1	$p = 0.113$
Carbonated beverage intake			
No	6 (24.0)	7 (24.1)	13 (24.1)
Yes	19 (76.0)	22 (75.9)	41 (75.9)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 0.001$	df = 1	$p = 0.991$
Soft drink intake			
No	7 (28.0)	8 (27.6)	15 (27.8)
Yes	18 (72.0)	21 (72.4)	39 (72.2)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 0.001$	df = 1	$p = 0.973$

Table 6 Dietary pattern and physical activity of the subjects before treatment (continued)

Characteristics	FOS groups number (%)	MOM group number (%)	Total number (%)
Fruit juice intake			
No	12 (48.0)	8 (27.6)	20 (37.0)
Yes	13 (52.0)	21 (72.4)	34 (63.0)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 2.399$	df = 1	$p = 0.121$
Snack intake			
No	3 (12.0)	1 (3.5)	4 (7.4)
Yes	22 (88.0)	28 (96.5)	50 (92.6)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 1.432$	df = 1	$p = 0.121$
How to go to school			
By car	12 (48.0)	17 (58.7)	29 (53.7)
By school bus	8 (32.0)	5 (17.2)	13 (24.1)
On foot	3 (12.0)	5 (17.2)	8 (14.8)
By motorcycle	2 (8.0)	2 (6.9)	4 (7.4)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 1.768$	df = 3	$p = 0.622$
Time spent in watching television per day			
< 1 hour	7 (28.0)	15 (51.7)	22 (40.7)
1-3 hours	9 (36.0)	9 (31.0)	18 (33.3)
3-5 hours	5 (20.0)	4 (13.8)	9 (16.7)
5-7 hours	2 (8.0)	0	2 (3.7)
> 7 hours	2 (8.0)	1 (3.5)	3 (5.6)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 5.085$	df = 4	$p = 0.279$
Time spent in playing computer per day			
< 1 hour	20 (80.0)	20 (69.0)	40 (74.1)
1-3 hours	4 (16.0)	8 (27.6)	12 (22.2)
3-5 hours	1 (4.0)	1 (3.4)	2 (3.7)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 1.043$	df = 2	$p = 0.594$

Table 6 Dietary pattern and physical activity of the subjects before treatment (continued)

Characteristics	FOS group	MOM group	Total
	number (%)	number (%)	number (%)
Time spent in reading cartoon per day			
< 1 hour	19 (76.0)	26 (89.7)	45 (83.3)
1-3 hours	4 (16.0)	1 (3.4)	5 (9.3)
3-5 hours	2 (8.0)	2 (6.9)	4 (7.4)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 2.607$	df = 2	$p = 0.272$
Time spent in outdoor activity per day			
< 1 hour	17 (68.0)	20 (69.0)	37 (68.5)
1-3 hours	8 (32.0)	8 (27.6)	16 (29.6)
3-5 hours	0	1 (3.4)	1 (1.9)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 0.952$	df = 2	$p = 0.621$
Number of days of exercise per week			
None	22 (88.0)	23 (79.3)	45 (83.3)
1-2 days	1 (4.0)	4 (13.8)	5 (9.3)
3-4 days	1 (4.0)	2 (6.9)	3 (5.7)
5-6 days	1 (4.0)	0	1 (1.9)
Total	25 (100.0)	29 (100.0)	54 (100.0)
	$\chi^2 = 2.875$	df = 3	$p = 0.411$

Table 7 Defecation pattern of the subjects in each treatment

Characteristics	FOS group number (%)		MOM group number (%)	
	Before treatment	The end of treatment	Before treatment	The end of treatment
Frequency of defecation				
< 3 times/week	25 (100.0)	0	29 (100.0)	1 (3.5)
3 times/week	0	4 (16.0)	0	1 (3.5)
4-6 times/week	0	18 (72.0)	0	23 (79.3)
1-2 times/day	0	3 (12.0)	0	4 (13.7)
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
Mean of frequency in defecation (times/week)	1.36	5.14	1.28	5.87
	χ_1^2 = NA		χ_2^2 = 3.27 (df = 3)	p = 0.361
	t_1 = 15.56 (df = 24)	$p < 0.001$	t_2 = 22.44 (df = 28)	$p < 0.001$
Characteristic of feces				
Separate hard lumps, like nut (type 1)	24 (96.0)	0	29 (100.0)	0
Sausage-shaped but lumpy (type 2)	1 (4.0)	0	0	0
Sausage-shaped but with cracks on surface (type 3)	0	0	0	0
Sausage-shaped or snake, smooth and soft (type 4)	0	18 (72.0)	0	18 (62.1)
Soft blobs/ mushy stool/ watery (type 5, 6, 7)	0	7 (28.0)	0	11 (37.9)
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
Mean of scale in stool consistency	1.80	4.45	1.55	4.58
	χ_1^2 = 1.18 (df = 1)	p = 0.277	χ_2^2 = 0.60 (df = 1)	p = 0.440
	t_1 = 22.32 (df = 24)	$p < 0.001$	t_2 = 17.45 (df = 28)	$p < 0.001$

$\chi_1^2, \chi_2^2, \chi_3^2, \chi_4^2$ = compare frequency between before treatment of two groups, the end of treatment of two groups, before and after treatment in the FOS group, and before and after treatment in the MOM group, respectively.
t_1^2, t_2^2 = compare mean between before and after treatment in the FOS group, and before and after treatment in the MOM group respectively.
NA = not available

Table 7 Defecation pattern of the subjects in each treatment (continued)

Characteristics	FOS group number (%)		MOM group number (%)	
	Before treatment	**The end of treatment**	**Before treatment**	**The end of treatment**
Frequency of straining during defecation				
None	1 (4.0)	25 (100.0)	1 (3.5)	29 (100.0)
A few time	2 (8.0)	0	1 (3.5)	0
Sometimes (about half of defecations)	1 (4.0)	0	1 (3.5)	0
Often (more than half of defecations)	2 (8.0)	0	0	0
Always	19 (76.0)	0	26 (89.5)	0
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
	$\chi_1^2 = 3.14$ (df = 4)	$p = 0.534$	$\chi_2^2 = NA$	
	$\chi_3^2 = 46.15$ (df = 4)	$p < 0.001$	$\chi_4^2 = 54.13$ (df = 3)	$p < 0.001$
Frequency of pain at anus during defecation				
None	1 (4.0)	25 (100.0)	2 (6.9)	29 (100.0)
A few time	2 (8.0)	0	1 (3.5)	0
Sometimes (about half of defecations)	2 (8.0)	0	1 (3.5)	0
Often (more than half of defecations)	2 (8.0)	0	4 (13.8)	0
Always	18 (72.0)	0	21 (72.4)	0
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
	$\chi_1^2 = 1.61$ (df = 4)	$p = 0.807$	$\chi_2^2 = NA$	
	$\chi_3^2 = 46.15$ (df = 4)	$p < 0.001$	$\chi_4^2 = 50.52$ (df = 4)	$p < 0.001$

$\chi_1^2, \chi_2^2, \chi_3^2, \chi_4^2$ = compare frequency between before treatment of two groups, the end of treatment of two groups, before and after treatment in the FOS group, and before and after treatment in the MOM group, respectively.
t_1^2, t_2^2 = compare mean between before and after treatment in the FOS group, and before and after treatment in the MOM group respectively.
NA = not available

Table 7 Defecation pattern of the subjects in each treatment (continued)

Characteristics	FOS group number (%)		MOM group number (%)	
	Before treatment	**The end of treatment**	**Before treatment**	**The end of treatment**
Frequency of feeling incomplete evacuation				
None	4 (16.0)	25 (100.0)	13 (44.8)	29 (100.0)
A few time	5 (20.0)	0	7 (24.1)	0
Sometimes (about half of defecations)	2 (8.0)	0	0	0
Often (more than half of defecations)	4 (16.0)	0	1 (3.5)	0
Always	10 (40.0)	0	8 (27.6)	0
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
	$\chi_1^2 = 8.87$ (df = 4)	$p = 0.064$	$\chi_2^2 = $ NA	
	$\chi_3^2 = 36.21$ (df = 4)	$p < 0.001$	$\chi_4^2 = 22.10$ (df = 3)	$p < 0.001$
Frequency of urge during defecation				
None	19 (76.0)	25 (100.0)	21 (72.4)	29 (100.0)
A few time	2 (8.0)	0	3 (10.3)	0
Sometimes (about half of defecations)	1 (4.0)	0	1 (3.5)	0
Often (more than half of defecations)	2 (8.0)	0	1 (3.5)	0
Always	1 (4.0)	0	3 (10.3)	0
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
	$\chi_1^2 = 1.34$ (df = 4)	$p = 0.854$	$\chi_2^2 = $ NA	
	$\chi_3^2 = 6.82$ (df = 4)	$p = 0.146$	$\chi_4^2 = 9.28$ (df = 4)	$p = 0.054$

$\chi_1^2, \chi_2^2, \chi_3^2, \chi_4^2$ = compare frequency between before treatment of two groups, the end of treatment of two groups, before and after treatment in the FOS group, and before and after treatment in the MOM group, respectively.
t_1^2, t_2^2 = compare mean between before and after treatment in the FOS group, and before and after treatment in the MOM group respectively.
NA = not available

Table 7 Defecation pattern of the subjects in each treatment (continued)

Characteristics	FOS group number (%)		MOM group number (%)	
	Before treatment	**The end of treatment**	**Before treatment**	**The end of treatment**
Time spent in each defecation				
< 5 minutes	14 (56.0)	18 (72.0)	12 (41.4)	23 (79.3)
5-9 minutes	5 (20.0)	7 (28.0)	9 (31.0)	6 (20.7)
10-14 minutes	1 (4.0)	0	1 (3.5)	0
15-19 minutes	2 (8.0)	0	0	0
> 20 minutes	3 (12.0)	0	7 (24.1)	0
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
	$\chi_1^2 = 4.63$ (df = 4)	$p = 0.328$	$\chi_2^2 = 0.40$ (df = 1)	$p = 0.531$
	$\chi_3^2 = 6.83$ (df = 4)	$p = 0.145$	$\chi_4^2 = 12.06$ (df = 3)	$p = 0.007$
Having abdominal pain during defecation				
No	5 (20.0)	23 (92.0)	9 (31.03)	27 (93.1)
Yes	20 (80.0)	2 (8.0)	20 (68.97)	2 (6.9)
Total	25 (100.0)	25 (100.0)	29 (100)	29 (100.0)
	$\chi_1^2 = 0.85$ (df = 1)	$p = 0.356$	$\chi_2^2 = 0.024$ (df = 1)	$p = 0.877$
	$\chi_3^2 = 26.30$ (df = 1)	$p < 0.001$	$\chi_4^2 = 23.73$ (df = 1)	$p < 0.001$

$\chi_1^2, \chi_2^2, \chi_3^2, \chi_4^2$ = compare frequency between before treatment of two groups, the end of treatment of two groups, before and after treatment in the FOS group, and before and after treatment in the MOM group, respectively.

t_1^2, t_2^2 = compare mean between before and after treatment in the FOS group, and before and after treatment in the MOM group respectively.

NA = not available

Table 7 Defecation pattern of the subjects in each treatment (continued)

Characteristics	FOS group number (%)		MOM group number (%)	
	Before treatment	**The end of treatment**	**Before treatment**	**The end of treatment**
Having flatulence during defecation				
No	23 (92.0)	23 (92.0)	26 (89.7)	29 (100.0)
Yes	2 (8.0)	2 (8.0)	3 (10.3)	0
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
	$\chi_1^2 = 0.09$ (df = 1)	$p = 0.767$	$\chi_2^2 = 2.41$ (df = 1)	$p = 0.121$
	$\chi_3^2 = $ NA		$\chi_4^2 = 3.16$ (df = 1)	$p = 0.075$
Having incontinent during defecation				
No	22 (88.0)	25 (100.0)	25 (86.2)	29 (100.0)
Yes	3 (12.0)	0	4 (13.8)	0
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
	$\chi_1^2 = 0.04$ (df = 1)	$p = 0.845$	$\chi_2^2 = $ NA	
	$\chi_3^2 = 3.19$ (df = 1)	$p = 0.074$	$\chi_4^2 = 4.30$ (df = 1)	$p = 0.038$
Feeling pain at anus during defecation				
No	0	25 (100.0)	0	29 (100.0)
Yes	25 (100.0)	0	29 (100.0)	0
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
	$\chi_3^2 = 50$ (df = 1)	$p < 0.001$	$\chi_4^2 = 58$ (df = 1)	$p < 0.001$

$\chi_1^2, \chi_2^2, \chi_3^2, \chi_4^2 = $ compare frequency between before treatment of two groups, the end of treatment of two groups, before and after treatment in the FOS group, and before and after treatment in the MOM group, respectively.
$t_1^2, t_2^2 = $ compare mean between before and after treatment in the FOS group, and before and after treatment in the MOM group respectively.
NA = not available

Table 7 Defecation pattern of the subjects in each treatment (continued)

Characteristics	FOS group number (%)		MOM group number (%)	
	Before treatment	The end of treatment	Before treatment	The end of treatment
Having blood-streaked stool				
No	17 (68.0)	25 (100.0)	14 (48.3)	29 (100.0)
Yes	8 (32.0)	0	15 (51.7)	0
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
	$\chi_1^2 = 2.14$ (df = 1)	$p = 0.144$	$\chi_2^2 = $ NA	
	$\chi_3^2 = 9.52$ (df = 1)	$p = 0.002$	$\chi_4^2 = 20.23$ (df = 1)	$p < 0.001$
Frequency of withhold feces				
None	6 (24.0)	20 (80.0)	3 (10.3)	24 (82.8)
A few time	1 (4.0)	4 (16.0)	3 (10.3)	3 (10.3)
Sometimes (about half of defecations)	2 (8.0)	1 (4.0)	2 (6.9)	2 (6.9)
Often (more than half of defecations)	3 (12.0)	0	1 (3.5)	0
Most of the time	13 (52.0)	0	20 (69.0)	0
Total	25 (100.0)	25 (100.0)	29 (100.0)	29 (100.0)
	$\chi_1^2 = 4.21$ (df = 4)	$p = 0.378$	$\chi_2^2 = 0.55$ (df = 2)	$p = 0.761$
	$\chi_3^2 = 25.67$ (df = 4)	$p < 0.001$	$\chi_4^2 = 37.33$ (df = 4)	$p < 0.001$

$\chi_1^2, \chi_2^2, \chi_3^2, \chi_4^2$ = compare frequency between before treatment of two groups, the end of treatment of two groups, before and after treatment in the FOS group, and before and after treatment in the MOM group, respectively.
t_1^2, t_2^2 = compare mean between before and after treatment in the FOS group, and before and after treatment in the MOM group respectively.
NA = not available

4.2   The pattern of defecation

The key variables in this study that indicated alteration of defecation after treatments included frequency of defecation and the stool consistency.

4.2.1   Frequency of defecation

The frequency of defecation of the FOS and MOM groups increased when compared with baselines (Figure 6).   After two weeks, the frequency of defecation increased significantly ($p < 0.0001$) in both groups.   Also, after 6-week treatment, the frequency of defecation increased significantly ($p = 0.001$).   However, the significant difference between the FOS and MOM groups was not found in frequency of defecation at baseline, week 2 and week 6.
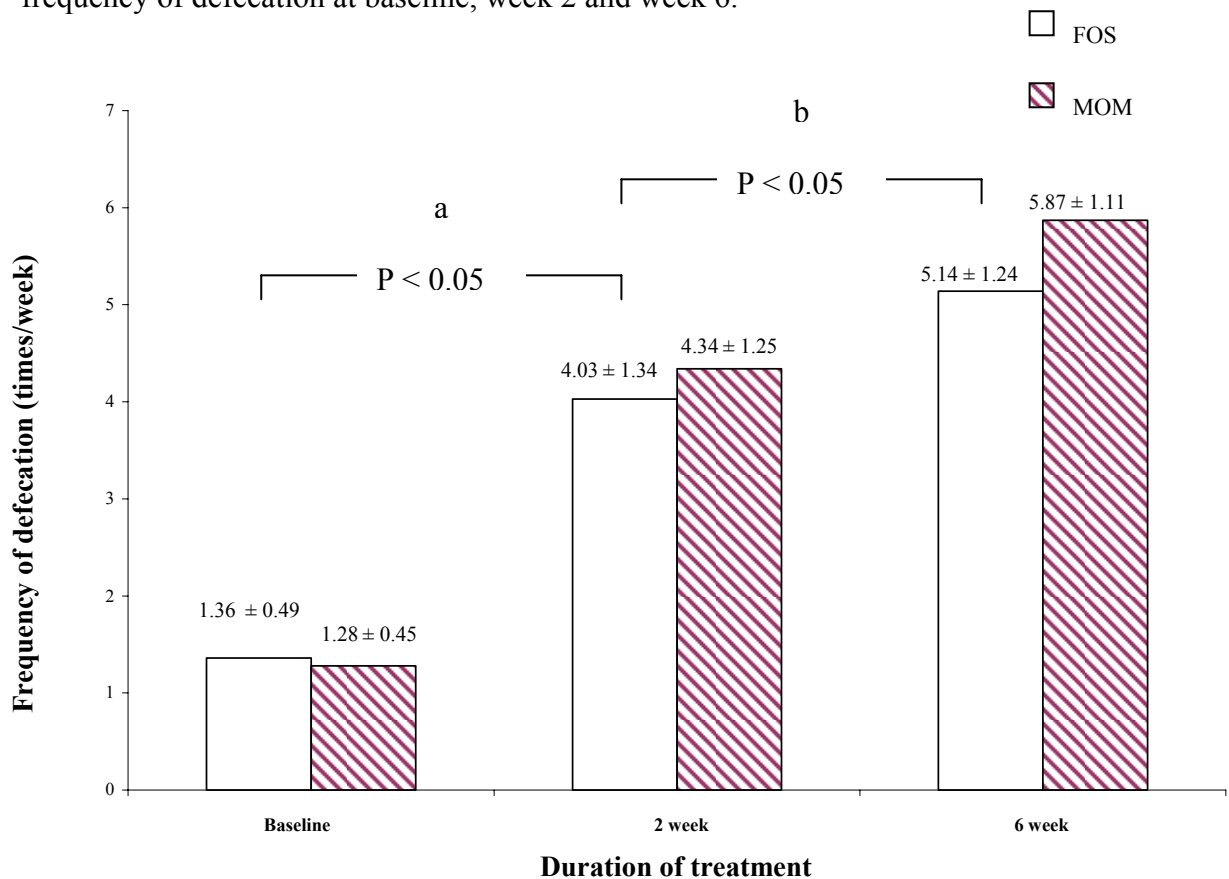
[a] Different from before treatment with $p < 0.05$
[b] Different from 2-week treatment with $p < 0.05$

Figure 6 Frequency of defecation in the FOS and MOM groups at baseline, 2 weeks and 6 weeks after treatments

4.2.2 The stool consistency

Figure 7 shows that the FOS and MOM groups had improved significantly on stool consistency when compared with baselines. The stool consistency was rated from 1-7 of scores (very hard to soft). For example, 1 point means hard stool like nut, 4 points means smooth and soft stool, and 7 points means watery stool. Before treatment the stools of the subjects in both groups looked like lumpy and hard feces (1.80 ± 0.58 and 1.55 ± 0.69 in the FOS and MOM groups, respectively). After 2 weeks, they looked smoother and softer (4.39 ± 0.64 and 4.64 ± 0.82 in the FOS and MOM groups respectively) and the same results were found at the end of the treatments. However, the FOS and MOM groups were not significantly different in stool consistency at baseline, week 2 and week 6.
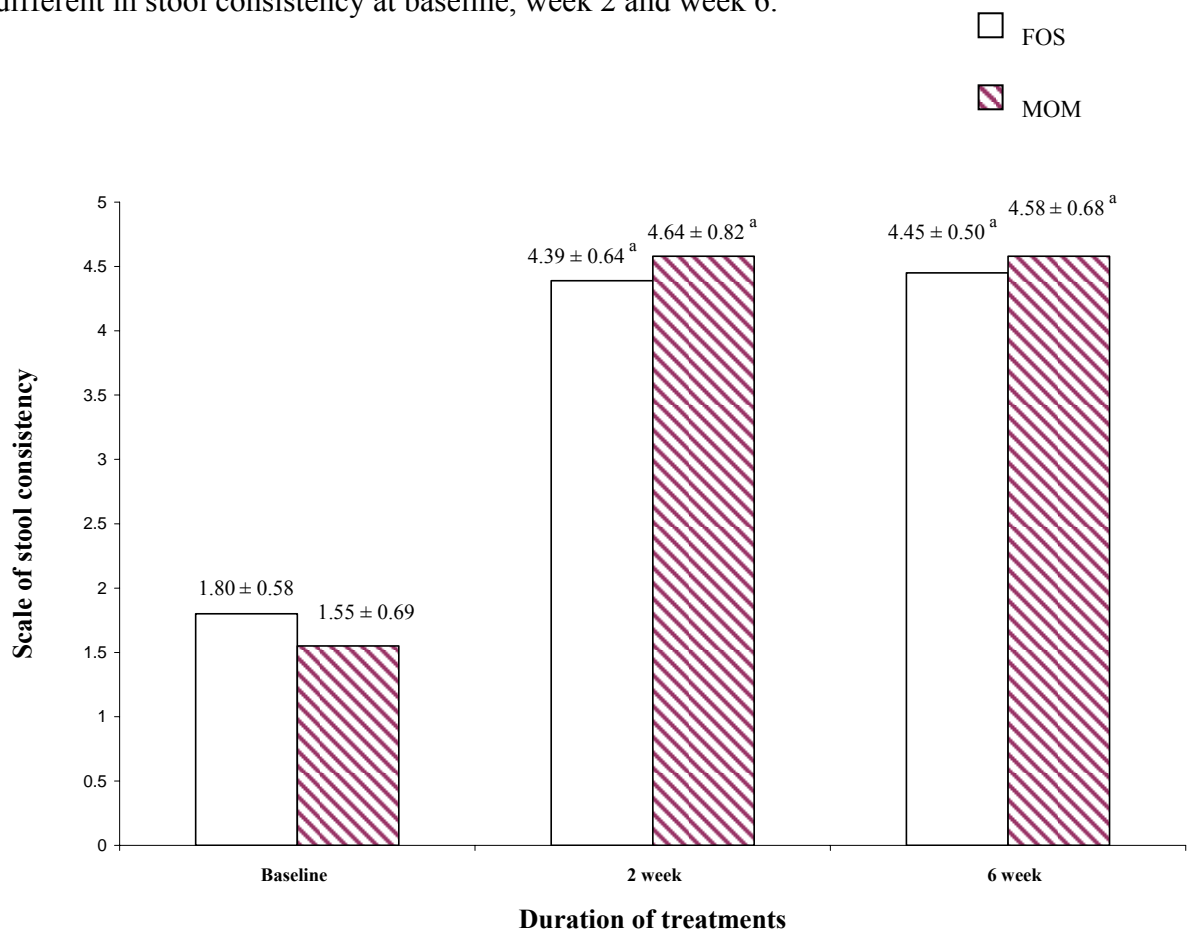
[a] Different from before treatment with $p < 0.05$

Figure 7 The stool consistency in the FOS and MOM groups at baseline, 2 weeks and 6 weeks after treatment

4.3   Dietary pattern of the subjects

The subjects were advised about proper food intake. Dietary pattern was assessed by 24-hour recall at the beginning of the study and 3-day food record at the last week of the intervention in both groups. All records were analyzed in term of energy, protein, fat, carbohydrate, fiber, and water intakes per day using the computerized program "Nutrisurvey" modified for Thai food by Tuntrongchitr (2005).

Dietary patterns of the subjects in the FOS and MOM groups at the beginning of the study were not significantly different. Before treatment, the amount of energy, carbohydrate, protein, fat, dietary fiber and water intakes per day in the both groups were not different ($p > 0.05$). After treatment, the amount of protein and fat intakes in the MOM group were significantly greater than those in the FOS group.   However, the increase in proportion of dietary fiber intake was observed in the both groups. (Table 8).

4.4   The growth rate of the subjects

The growth rate of the subjects were determined by weight and height measurements. The assessments were performed 3 times at baseline, week 2 and 6 of treatment. The values of weight and height were plotted as percentile on the growth charts (Pediatric Endocrine Society of Thailand for children 2-19 years old).

There were no differences in weight, height, and BMI between the FOS and MOM groups. The growth charts showed normal growth in the both groups with the percentile between P 75-90 and P 50-75 (Table 9)

Table 8 Energy distribution and nutrient intakes in the FOS and MOM groups before and after the treatments[1]

		Before the treatment[2]		After the 6-week treatment[3]	
		FOS group (n = 25)	**MOM group (n = 29)**	**FOS group (n = 25)**	**MOM group (n = 29)**
Total energy (kcal)		1042.80 ± 247.09	1075.40 ± 243.81	1507.80 ± 559.41	1599.90 ± 532.52
Protein	Energy (kcal)	291.56 ± 61.44	296.44 ± 109.20	325.52 ± 86.84 *	414.04 ± 156.88 *
	Weight (g)	72.89 ± 15.36	74.11 ± 27.30	81.38 ± 21.71 *	103.51 ± 39.22 *
Fat	Energy (kcal)	409.95 ± 214.29	398.43 ± 119.61	482.76 ± 269.82 *	631.44 ± 225.72 *
	Weight (g)	45.55 ± 23.81	44.27 ± 13.29	53.64 ± 29.98 *	70.16 ± 25.08 *
Carbohydrate	Energy (kcal)	422.24 ± 135.56	456.44 ± 181.88	688.20 ± 272.52	545.68 ± 216.72
	Weight (g)	105.56 ± 33.89	114.11 ± 45.47	172.05 ± 68.13	136.42 ± 54.18
Dietary fiber (g)[4]		8.01 ± 3.28	7.51 ± 3.77	8.43 ± 4.97	14.46 ± 4.98
Water (g)		939.50 ± 287.36	863.37 ± 216.52	1444.10 ± 451.83	1287.20 ± 347.08

[1] Mean ± SD
[2] Data derived from 24-hour recall food record
[3] Data derived from 3-day food record
[4] Dietary fiber in the FOS group was total fiber intake plus FOS 5 g/day

Table 9 Nutritional assessment of the subjects[1]

Assessments	FOS (n = 25)			MOM (n = 29)		
	0 week	2 weeks	6 weeks	0 week	2 weeks	6 weeks
Weight (kg)	25.54 ± 10.1	25.9 ± 10.2	26.22 ± 10.33	21.89 ± 8.43	22.36 ± 8.33	22.47 ± 8.3
Height (cm)	121.28 ± 18.59	121.9 ± 18.64	122.3 ± 18.56	115.86 ± 13.08	116.36 ± 13.04	116.47 ± 12.97
BMI	16.56 ± 2.4	16.77 ± 2.35	16.86 ± 2.36	15.89 ± 3.48	16.11 ± 3.34	16.18 ± 3.33
Weight for age[2]	P75-90	P75-90	P75-90	P50-75	P50-75	P50-75
Height for age[2]	P75-90	P75-90	P75-90	P50-75	P50-75	P50-75
Weight for height[2]	P75-90	P75-90	P75-90	P50-75	P50-75	P50-75

Each treatment in mean value were not different at 2 and 6 weeks from baseline
[1] mean ± SD
[2] Percentile of growth value derived from the growth chart of Pediatric Endocrine Society of Thailand for children 2-19 years old: P10-90 = normal growth.

4.5 The adverse effects of the FOS and MOM treatments

Ten subjects (18.5%) reported adverse effects of the treatments [6 subjects (24.0%) and 4 subjects (13.8%) in the FOS and MOM groups, respectively]. These adverse effects included abdominal pain, decrease appetite, diarrhea, flatulence, nausea, pass wind, and vomiting (Table 10). There were no serious adverse effects found in this study.

Table 10 Adverse effects of the treatments

Adverse effects	FOS[1]	MOM[2]
Abdominal pain	2	2
Decrease appetite	3	0
Diarrhea	1	1
Flatulence	2	0
Nausea	1	0
Pass wind	3	3
Vomiting	0	1

[1] Number of adverse effect from 6 patients in the FOS groups
[2] Number of adverse effect from 4 patients in the MOM groups

4.6   The evaluation of adherence to treatment

Compliance of the treatment was evaluated by calculation the amount of FOS or MOM intakes throughout the study. It was found that the subjects had compliance with treatments more than 95% (Appendix B).

CHAPTER 5

DISCUSSION

This study investigated the efficacy of fructooligosaccharide (FOS) treatment compared with milk of magnesia (MOM) treatment in constipated pediatric patients at Queen Sirikit National Institute of Child Health.

5.1   Characteristics of the subjects

The data from the Queen Sirikit National Institute of Child Health showed the number of visits to physicians for constipation between 2002 to 2006. A surprising finding was the continuing increase in incidence of physician visit.   Most of the pediatric constipated patients were school-age children, with the average age of 6 years old. Proportion of boys and girls was approximately 2:1. It was consistent with studies of Lorenzo (2001) and Abi-Hanna and Lake (1998) that childhood constipation in school-age probably occurs much more commonly in boys than girls. Causes of constipation in school-age child were inadequate fluid intake and/or consumption of diet lacking of fiber because most of them often consumed carbonated beverages, soft drinks, fruit juices, and snacks. Their physical inactivities may be related to reduced colonic motility (Borowitz et al., 2005). In addition, these children often withheld their feces because they suffered pain with the passage of stool. Withholding feces can lead to prolonged fecal stasis in colon, reabsorption of fluid and increase in the size and consistency of the stools. The passage of large and hard stools that painfully stretch the anus may frighten the child resulting in a fearful determination to avoid all defecations (Partin et al., 1992; Borowitz et al., 2003; Naspghan Constipation Guideline Committee, 2006). After several days without a

bowel movement, irritability, abdominal distension, cramps, encopresis (fecal soiling), and decrease in food intake may occur (Naspghan Constipation Guideline Committee, 2006). Once these problems accumulated, the treatment from the physicians is often required.

5.2   Effect of fructooligosaccharide supplementation on pediatric constipation compared with milk of magnesia treatment

In this study, the subjects in the FOS group received FOS supplement about 5 g/day. After treatment, it was found that FOS could induce frequency of defecations. The frequency elevated from 1 to 4 and 5 stools/week at 2 and 6 weeks respectively. The stool consistency was less likely to be described as "hard", and more likely to be described as "soft" or "loose" in the FOS group. It was consistent with other clinical trials. Kleessen et al. (1997) studied in constipated elderly patients who received 20-40 g/day of FOS for 19 days. The result showed an increase in frequency and softer stool consistency when compared with before treatment. Gibson et al (1995) found that treatment of 15 g/day of FOS for 15 days in healthy volunteers could increase their stool outputs significantly. Chen et al. (2000) studied in constipated elderly patients receiving 10 g/day of FOS for 30 days. It was found that their stool outputs increased significantly. In case of infants, supplementation with 1.5-3 g/day of FOS induced an increase in stool outputs and softer stools (Moore et al., 2003; Euler et al., 2005; Bettler and Euler, 2006). Furthermore, the subjects in this study who received FOS had not painfully stretch the anus, could easily passage of feces in defecation without force, had reduction of feeling incomplete during defecation and frequency of withholding, and did not have the blood-streaked stool. It indicated that FOS

supplement could improve the symptoms of constipation. This result was also found in the MOM treatment group.

FOS are considered as prebiotics because they are not hydrolyzed in the upper gastrointestinal tract. Their chemical structures escape digestion by pancreatic and small-bowel enzymes and therefore arrive large bowel (Cummings et al., 2001). They are nondigestible oligosaccharides that have positive effect on intestinal transit and stool consistency. FOS are soluble dietary fiber, which reduce fecal pH, increase the water/holding capacity of stool and faecal weight, and decrease intestinal transit time. Furthermore, they are fermented and produce gases (CO_2, H_2, CH_4), lactic acid, short chain fatty acids (SCFA) and stimulate the growth of probiotic bacteria, such as bifidobacteria (Walker and Duffy, 1998; Duggan et al., 2002; Cherbut 2002; Benninga, Candy and Taminiau, 2005). The improved defecation in constipated individuals may be due to these specific properties of FOS. Dose of FOS supplementation in constipated patients varied and all doses used in previous studies could induce stool frequency (Chen et al., 2000; Kleessen et al., 1997; Euler et al., 2005; Bettler and Euler, 2006). In the present study, it was found that 5 g/day of FOS had efficacy in alleviation of constipation and the results were similar to MOM treatment.

The results from the present study showed that the changes in frequency of defecations and stool consistency in the FOS and MOM groups were not significantly different. The adherence of each treatment was not different either. Several researches had studied about efficacy of the other prebiotics (lactulose) or various laxatives in pediatric constipation such as PEG 3350 and sorbitol. Lactulose is not absorbed by the small bowel and acts as an osmotic agent. It has been effectively used for long-term maintenance therapy in children, but in some children may find

flatulence, bloating and abdominal cramp because it is fermented in the colon by colonic bacteria (Pashankar and Tolia, 2004). One of the studies compared efficacy of PEG 3350 with lactulose. There were no differences in stool frequency and consistency between the both laxatives, but PEG 3350 could reduce significantly the total colonic transit time (Gremse, Hixan and Crutchfield, 2002). When the treatment was extended to 8 weeks, it was found that PEG 3350 was more effective than lactulose (Voskuijl et al., 2004). The other study found that efficacy and adverse effects of lactulose and sorbitol were not different (Ledele et al., 1990). However, the effective treatment of chronic constipation is not only laxative use but also behavioral modification which includes dietary advice, toilet training, and increased intake of fluids.

Adverse effects of FOS treatment observed in this study included abdominal pain, flatulence, decrease in appetite, diarrhea, nausea, pass wind, and vomiting. These problems were also found in patients with MOM treatment. However, the number of patients who suffered from side effects in the FOS group was more than in the MOM group. The adverse effects of FOS found in the present study were similar to those found in the previous study of Zheng et al. (1999) which using 2 g/day of FOS. It was concluded that the FOS intolerance were generally presented as GI symptoms such as flatulence, bloating, abdominal distension, and rumbling. Nonetheless, these adverse effects were common and dependent on dosage of FOS (Kleessen et al., 1997). Numerous publication in clinical journals documented the studies on the safety of FOS in normal subjects and patients with disease states (Price, Schwarthz and Hoyt, 1978; Yamashita, Kawai and Itakura, 1984; Zheng et al., 1999). These individuals in different ages have provided additional assurances of safety of inulin and FOS (Roberfroid, 1993; Carabin and Flamm, 1999).

Both groups of treatment were similar efficacy but it seem to be that FOS had more adverse effects. However, FOS had more benefit because they are prebiotic that affect the host by selectively stimulating the growth and activity of bacteria in colon such as *Bifidobacterium spp.* which could be induce immune in the body, inhibit growth of pathogen and reduce diarrhea from pathogen when receiving long-term treatment of antibiotics (Kaur and Gupta, 2002). MOM was osmotic laxative which increased water in stool to help defecation but it has caution in infant and patient with renal impairment. It rarely induces hypermagnesemia, hypophosphatemia, secondary hypocalcemia and leads to respiratory depression (Biggs and Dery, 2006).

Dosage of FOS using in the study was 5 g/day because previous studies which studied in infant in dosage of 3 g/day did not induce intestinal obstruction (Bettler and Euler, 2006; Euler et al., 2005). The other study using 10 g/day of FOS in elderly constipated patient who received showed had the efficacy of FOS in constipation treatment (Chen et al., 2000).

5.3   Dietary intake pattern of the subjects

In this study, the amounts of total energy and other nutrients intake per day were estimated by food record. The nutrition status of the subjects was also assessed. The researcher gave advices to the subjects and their parents about dietary intake and behavioral modifications. A proper dietary pattern includes increasing fluid and dietary fiber intakes to meet the recommended amounts for children older than 2 years (age plus 5 g/day) (McClung et al., 1995; ADA, 2002). These advices may help relieve constipation and consequently promote food intake as decreased appetite was common in constipated patients. The results showed increases in intake of total energy, protein, fat, carbohydrates, dietary fiber, and water in all participants when

compared with baseline. However, the amount of total energy and carbohydrate intakes of all patients were equally to the recommendation (1,400-1,700 and 1,400-1,600 kcal/day in males and females respectively, and 158-234 g/day of carbohydrate), but the amounts of protein and lipid intake were greater than recommendation (28-41 and 39-66 g/day respectively) (The committee on recommended daily allowances. 2003). In addition, the amount of dietary fiber intake in all subjects were in the recommended ranges, and no difference was found between the FOS and MOM groups.

5.4   Nutritional status of the subjects

The assessment of nutrition status of the subjects was performed. Most constipated children often have decreased appetite because they usually from vague chronic abdominal pain. The weight loss may be found in these patients but it dose not interfere the growth development (Loening-Baucke, 1993). In this study, FOS and MOM did not interfere the growth of the subjects. A few studies also demonstrated normal growth development of 6-24 months aged children with FOS supplementation at dose 2 g/day (Walligora-Dupriet et al., 2007; Zheng et al., 2006).

However, this study had treatment in short duration (6 weeks) that could not interpreted FOS was effectively using in chronic constipation patients because the constipated patients must be treated in long term at less 6 months and monitor the patient with change behavior and together.

Management of constipation generally includes both nonpharmacologic and pharmacologic measures. Goals of the management are improving symptoms, restoring normal bowel function, and facilitating defecation. Patients and their parents should be educated on behavioral training such as the routine of dietary fiber

intake, fluid intake, exercise, and toilet training (on the regular times). In addition, some patients who do not respond to the treatment program may be performed with obvious emotional disturbance or anxious in defecation. That should be treated by a psychiatrist or behavioralist together with pharmacologic measure (Felt et al., 1999; Walker et al., 2004; Bleser et al., 2005).

CHAPTER 6

CONCLUSION

This research studied the efficacy of FOS compared with MOM treatment in constipated patients at Queen Sirikit National Institute of Child Health. The subjects received either FOS or MOM treatment for 6 weeks and were evaluated the treatment efficacy in term of frequency of defecation, stool consistency, straining, pain during defecation, and adverse effects. Nutritional status and dietary intake pattern of the subjects were also assessed. The results showed the improvement of constipation after treatment with FOS, and the same result was found in treatment with MOM. The frequency of defecation increased and the stool consistency looked like sausage-shaped or snake, smooth and soft. Moreover, the subjects did not get strain and pain during defecation. Nevertheless, both FOS and MOM induced non-serious adverse effects during treatment such as abdominal pain, decreased appetite, diarrhea, flatulence, nausea and pass wind. All subjects were in normal range of growth development and their dietary intake increased, especially dietary fibers and fluids. The results in this study indicated that FOS was as well efficacious and safe as MOM in treatment for children with constipation, therefore FOS may be an alternative treatment for constipation. However, the dosage of FOS may be adjusted for tolerance in each patient. In addition, nutrition promotion is important for children to modify dietary intake pattern and related behaviors.

Recommendation for future research

1. Dosage of FOS supplementation should be adjusted in order to reduce the adverse effects.

2. Duration of FOS supplementation should be increased together with dietary fiber intake to recover constipation.

3. Efficacy and safety of FOS supplementation should be studied in other groups of constipated patients such as infants or toddlers or elderly.

4. The constipated patients should be monitored the recovery of constipation after treatment in long term period.

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Appendices

Appendix A

Estimation of food intake

Estimation of food intake

Twenty-four-hour records and three-day food records were done by the subjects or their parents. They were instructed how to record a three-day dietary intake (1 weekend day and 2 weekdays). The example of dietary record and form to fill were given to each subject (Appendix B). All items and portions of food consumed including name and method of preparation and cooking were asked to record. The subjects estimated food portion size using standard household measuring cups and spoons.

Portion size records were converted into gram of foods. The food records were analyzed for total food energy intake and its distribution from protein, fat, and carbohydrate. The nutrients consumed were analyzed by the computerized program "Nutrisurvey" modified for Thai food by Associate Professor Rungsunn Tuntrongchitr, Faculty of Tropical Medicine, Mahidol University.

Quantity of energy, protein, fat and carbohydrate per day were derived from twenty-four-hour record and three-day food records, and all amount of nutrients were compared with Dietary Requirements Intakes (DRIs) from Food and nutrition Board, Institute of Medicine, National Academies in Table (Lucas, 2003).

Table A-1 Dietary Reference Intake (DRIs) recommended intakes each age of children

Life-stage group	Energy (kcal/day)		Protein (g/day)	Fat (g/day)	Carbohydrate (g/day)
	Male	Female			
4-8 years	1,742	1,642	19	130	25-35
9-13 years	2,279	2,071	34	130	25-35

From Lucas, 2003.

Appendix B

- **Growth chart**

- **Questionnaire**

- **Defecation record**

- **Dietary record**

The growth chart on the National Growth References for children under 20 years of age from Nutrition Division, Department of Health, Ministry of Public Health. Thailand, 1999

Boys aged 2-19 years: height and weight

Data source: National Growth References for Children Under 20 Years of Age, 1999
Nutrition Division, Department of Health, Ministry of Public Health, Thailand.

T01-61
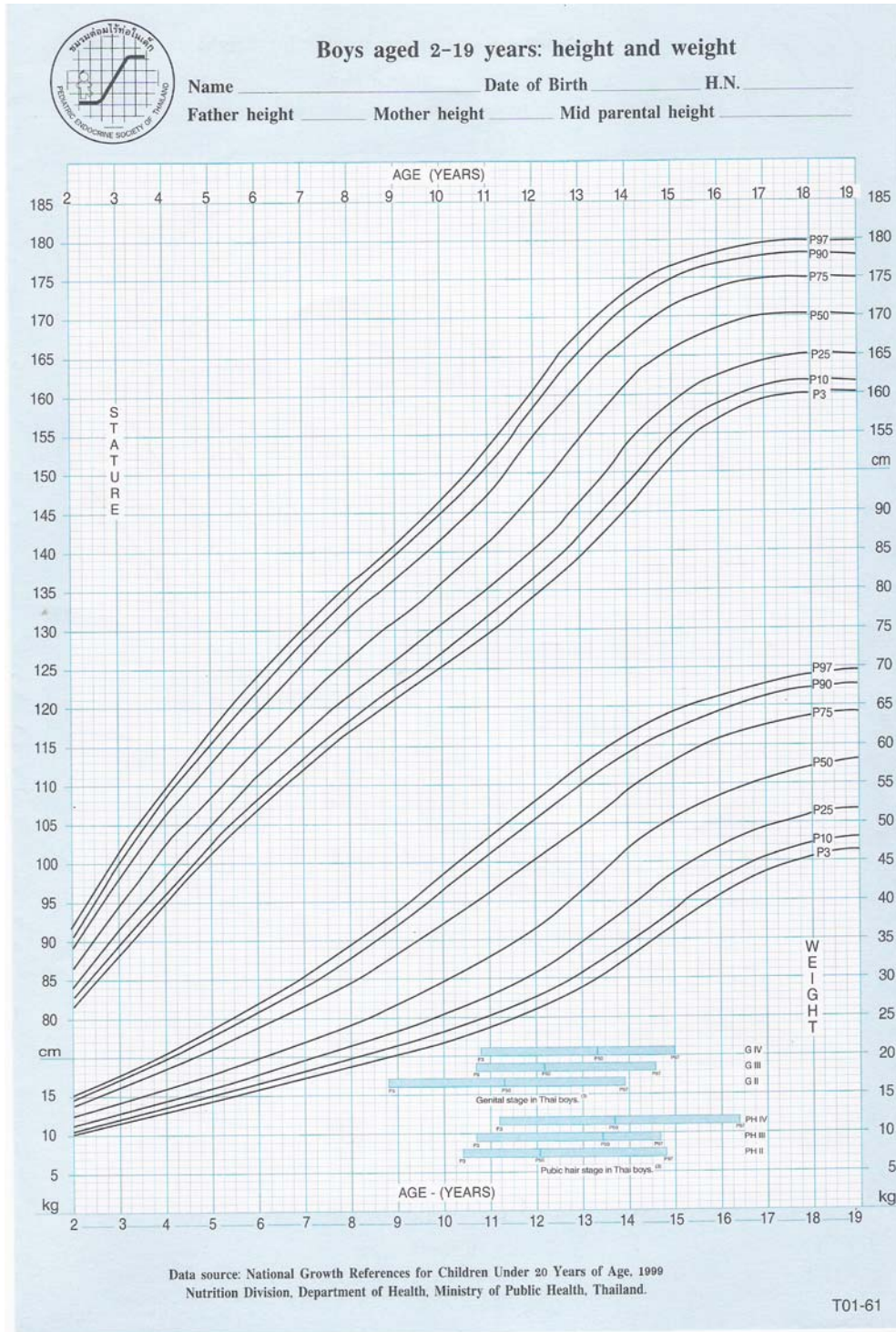
Girl aged 2-19 years: height and weight

Name _____ Date of Birth _____ H.N. _____

Father height _____ Mother height _____ Mid parental height _____
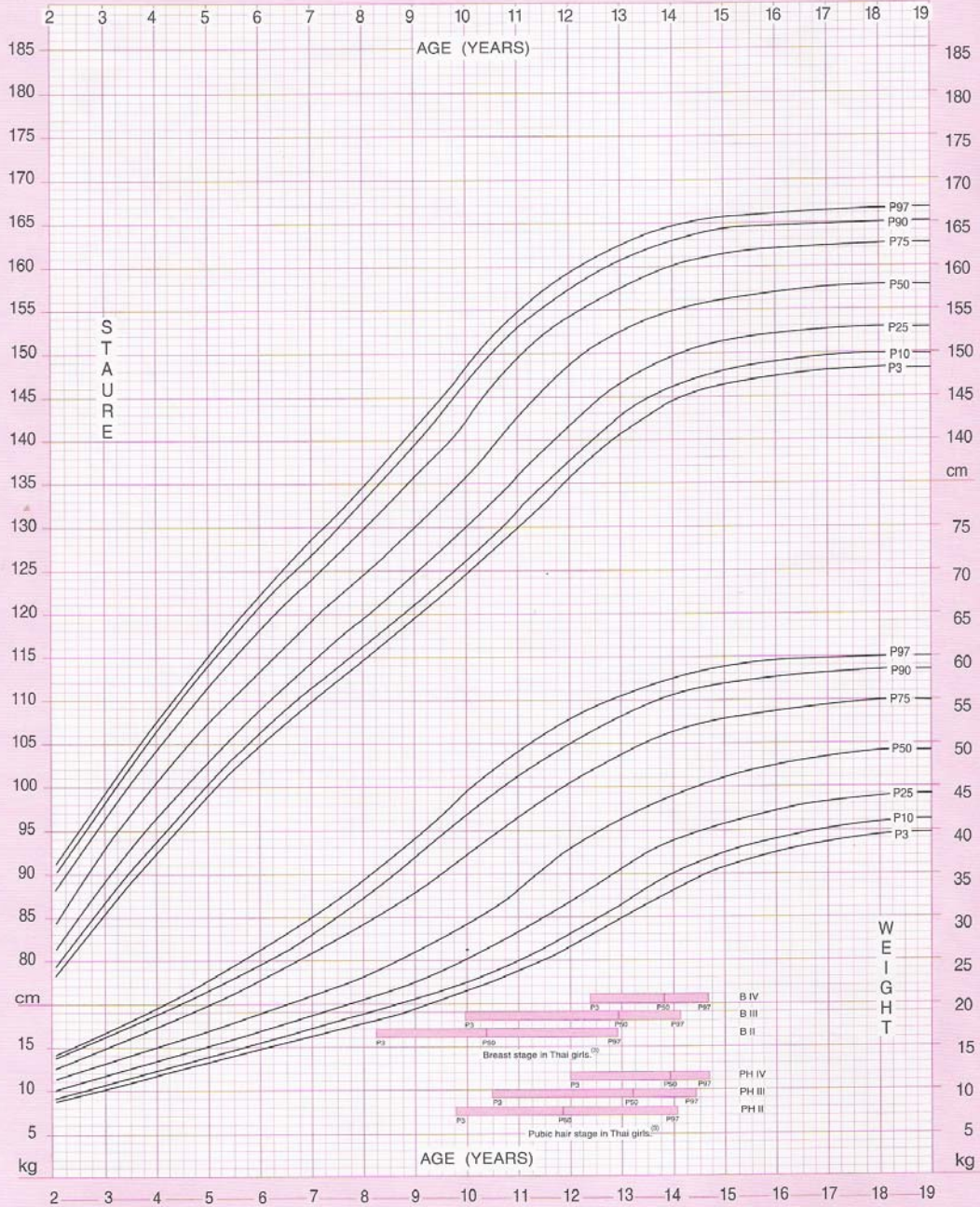
Data source: National Growth References for Children Under 20 Years of Age, 1999
Nutrition Division, Department of Health, Ministry of Public Health, Thailand.

T01- 62

Case No……..

แบบบันทึกข้อมูลผู้ป่วย

ส่วนที่ 1 ข้อมูลทั่วไปของผู้ป่วย

1. เพศ ☐ 1) ชาย ☐ 2) หญิง

2. อายุ .... ปี (วันเกิด ....)

3. น้ำหนัก .... กิโลกรัม ส่วนสูง .... เซนติเมตร (BMI .... kg/m^2)

4. ระดับการศึกษา

☐ 1) ยังไม่เข้าเรียนหนังสือ ☐ 2) อนุบาล

☐ 3) ประถมศึกษาปีที่ 1-3 ☐ 4) ประถมศึกษาปีที่ 4-6

☐ 5) มัธยมศึกษาปีที่ 1-3

5. ประเภทผู้ป่วย

☐ 1) ชำระเงิน ☐ 2) เบิกต้นสังกัด

☐ 3) โครงการ 30 บาท ☐ 4) อื่นๆ (ระบุ) ....

6. ประวัติการแพ้อาหารหรือยา (ระบุชื่อ และลักษณะอาการแพ้)

7.1) …………………………………… อาการแพ้ ....

7.2) …………………………………… อาการแพ้ ....

7. ประวัติการเจ็บป่วยหรือผ่าตัด (เรียงลำดับจากอดีตจนปัจจุบัน รวมทั้งระยะเวลาที่เจ็บป่วย)

8.1) …………………………………………………………… ระยะเวลา .... ปี

8.2) …………………………………………………………… ระยะเวลา .... ปี

8. ผู้ดูแลเด็กโดยส่วนใหญ่

☐ 1) บิดามารดา ☐ 2) ญาติพี่น้อง

☐ 3) พี่เลี้ยงเด็กในบ้าน ☐ 4) สถานที่รับเลี้ยงเด็ก

☐ 5) อื่นๆ (ระบุ)...............................

9. โรคประจำตัว

☐ 1) ไม่มีโรคประจำตัว ☐ 2) โรคภูมิแพ้

☐ 3) โรคหัวใจ ☐ 4) โรคต่อมไร้ท่อ

☐ 5) อื่นๆ (ระบุ)...............................

ส่วนที่ 2 ข้อมูลประเมินจำนวนยาที่ได้รับ

ข้อมูล	ครั้งที่ 1 (วันที่ 1 ของการวิจัย)	ครั้งที่ 2 (วันที่ 14 ของการวิจัย)	ครั้งที่ 3 (วันที่ 44 ของการวิจัย)	หมายเหตุ
วันที่นัดตรวจ				
วันที่มาตรวจจริง				
น้ำหนัก (กิโลกรัม)				
ความสูง (เซนติเมตร)				
BMI (kg/m^2)				
ชนิดยาที่ได้รับ (MOM/ FOS)				
จำนวนยาที่ให้				
จำนวนยาที่เหลือ				
จำนวนที่ใช้ไป				

ส่วนที่ 3 ข้อมูลเกี่ยวกับแบบแผนการบริโภคอาหาร กิจกรรมประจำวัน

ส่วนที่ 3.1 ข้อมูลเกี่ยวกับแบบแผนการบริโภคอาหาร

1. ส่วนใหญ่ เด็กรับประทานอาหารแบบใด

☐ 1) ทำอาหารรับประทานเองที่บ้าน

☐ 2) ซื้ออาหารปรุงสำเร็จรูป รับประทานที่บ้าน

☐ 3) รับประทานอาหารที่ปรุงสำเร็จนอกบ้าน

☐ 4) อาหารสำเร็จรูป เช่น บะหมี่กึ่งสำเร็จรูป อาหารกระป๋อง หรือโจ๊กสำเร็จรูป

☐ 5) อื่นๆ (ระบุ).......................................

2. การรับประทานอาหารที่มีเส้นใยอาหาร (เช่น ผัก ผลไม้ ถั่วหรือธัญพืชชนิดต่างๆ) บ่อยแค่ไหน

☐ 1) นานๆ ครั้ง (1-2 ครั้งต่อสัปดาห์)

☐ 2) บางครั้ง (3-4 ครั้งต่อสัปดาห์)

☐ 3) บ่อยครั้ง (5-6 ครั้งต่อสัปดาห์)

☐ 4) ประจำทุกวัน

3. ปริมาณการรับประทานอาหารที่มีเส้นใยอาหาร (เช่น ผัก ผลไม้ ถั่วหรือธัญพืชชนิดต่างๆ) ใน 1 วัน

☐ 1) ไม่มีเส้นใยอาหารเลย

☐ 2) น้อยกว่าครึ่งหนึ่งของอาหารที่รับประทานใน 1 วัน

☐ 3) ประมาณครึ่งหนึ่งของอาหารที่รับระทานใน 1 วัน

☐ 4) มากกว่าครึ่งหนึ่งของอาหารที่รับประทานใน 1 วัน

4. โดยปกติมีการดื่มน้ำ (ยกเว้นน้ำอัดลม น้ำผลไม้ น้ำหวาน) ปริมาณวันละเท่าไร

☐ 1) น้อยกว่า 1,000 มิลลิตรต่อวัน (น้อยกว่า 4 แก้วต่อวัน)

☐ 2) มากกว่า 1,000 มิลลิตรต่อวัน (มากกว่า 4 แก้วต่อวัน)

☐ 3) มากกว่า 1,500 มิลลิตรต่อวัน (มากกว่า 6 แก้วต่อวัน)

5. มีการดื่มน้ำอัดลมหรือไม่ ☐ 1) ไม่ดื่ม ☐ 2) ดื่ม (ระบุความถี่)........................

6. มีการดื่มน้ำหวานหรือไม่ ☐ 1) ไม่ดื่ม ☐ 2) ดื่ม (ระบุความถี่)........................

7. มีการดื่มน้ำผลไม้หรือไม่ ☐ 1) ไม่ดื่ม ☐ 2) ดื่ม (ระบุความถี่)........................

8. มีการบริโภคขนมขบเคี้ยวหรือไม่ ☐ 1) ไม่บริโภค ☐ 2) บริโภค (ระบุความถี่)...................

ส่วนที่ 3.2 กิจกรรมประจำวัน (วันหยุดเสาร์-อาทิตย์ หรือวันหยุดนักขัตฤกษ์)

1. การเดินทางไปกลับโรงเรียนส่วนใหญ่เดินทางแบบใด (กรณีเด็กที่เริ่มเรียนแล้ว)

☐ 1) รถยนต์ส่วนตัว ☐ 2) รถโรงเรียน

☐ 3) รถประจำทาง ☐ 4) การเดินไปโรงเรียน

☐ 5) อื่นๆ (ระบุ)...............................

2. การนั่งดูโทรทัศน์บ่อยแค่ไหน

☐ 1) น้อยกว่า 1 ชั่วโมง ☐ 2) 1- น้อยกว่า 3 ชั่วโมง

☐ 3) 3- น้อยกว่า 5 ชั่วโมง ☐ 4) 5- น้อยกว่า 7 ชั่วโมง

☐ 5) มากกว่า 7 ชั่วโมง

3. การนั่งเล่นคอมพิวเตอร์หรือเกมส์บ่อยแค่ไหน

☐ 1) น้อยกว่า 1 ชั่วโมง ☐ 2) 1- น้อยกว่า 3 ชั่วโมง

☐ 3) 3- น้อยกว่า 5 ชั่วโมง ☐ 4) 5- น้อยกว่า 7 ชั่วโมง

☐ 5) มากกว่า 7 ชั่วโมง

4. การอ่านหนังสือ/การ์ตูนบ่อยแค่ไหน

☐ 1) น้อยกว่า 1 ชั่วโมง ☐ 2) 1- น้อยกว่า 3 ชั่วโมง

☐ 3) 3- น้อยกว่า 5 ชั่วโมง ☐ 4) 5- น้อยกว่า 7 ชั่วโมง

☐ 5) มากกว่า 7 ชั่วโมง

5. การวิ่งเล่นนอก/ในบ้านบ่อยแค่ไหน

    ☐ 1) น้อยกว่า 1 ชั่วโมง   ☐ 2) 1- น้อยกว่า 3 ชั่วโมง

    ☐ 3) 3- น้อยกว่า 5 ชั่วโมง   ☐ 4) 5- น้อยกว่า 7 ชั่วโมง

    ☐ 5) มากกว่า 7 ชั่วโมง

6. ใน 1 สัปดาห์มีการออกกำลังกายเป็นระยะเวลากี่วัน

    ☐ 1) ไม่มีการออกกำลังกาย   ☐ 2) 1-2 วัน

    ☐ 3) 3-4 วัน   ☐ 4) 5-6 วัน

    ☐ 5) ทุกวัน

7. ถ้ามีการออกกำลังกาย ในแต่ละครั้งเป็นระยะเวลานานกี่นาที

    ☐ 1) น้อยกว่า 15 นาที   ☐ 2) 16-30 นาที

    ☐ 3) 31-45 นาที   ☐ 4) 46-60 นาที

    ☐ 5) มากกว่า 60 นาที

ส่วนที่ 4 ข้อมูลกับแบบแผนการถ่ายอุจจาระ 3 เดือน และ 1 เดือน ก่อนเข้าร่วมการวิจัย

ส่วนที่ 4.1 ข้อมูลกับแบบแผนการถ่ายอุจจาระ 3 เดือน ก่อนเข้าร่วมการวิจัย

1. ในระยะเวลา 3 เดือนที่ผ่านมา มีการถ่ายอุจจาระบ่อยมากแค่ไหน

    ☐ 1) มากกว่า 2 ครั้งต่อวัน

    ☐ 2) 1-2 ครั้งต่อวัน

    ☐ 3) 4-6 ครั้งต่อสัปดาห์ (เกือบทุกวัน)

    ☐ 4) 3 ครั้งต่อสัปดาห์ (วันเว้นวัน)

    ☐ 5) น้อยกว่า 3 ครั้งต่อสัปดาห์

2. ส่วนใหญ่อุจจาระมีลักษณะอย่างไร

    ☐ 1) ก้อนนิ่ม ไม่เป็นลำ/เหลว/คล้ายโคลน

    ☐ 2) ลำยาวอ่อนนุ่ม

    ☐ 3) ลำยาวคล้ายไส้กรอก

    ☐ 4) ลำยาวแข็ง

    ☐ 5) ก้อนแข็ง ไม่เป็นลำ คล้ายขี้แพะหรือเม็ดถั่ว

3. เด็กต้องออกแรงเบ่งมากกว่าปกติ ขณะถ่ายอุจจาระบ่อยครั้งแค่ไหน

    ☐ 1) ไม่ต้องเบ่งเลย

    ☐ 2) นานครั้ง

    ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่งของการถ่ายอุจจาระ)

    ☐ 4) บ่อยครั้ง (มากกว่าครึ่งของการถ่ายอุจจาระ)

    ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

4. มีอาการปวดก้น(รูทวารหนัก) ขณะถ่ายอุจจาระบ่อยครั้งแค่ไหน

     ☐ 1) ไม่มีอาการเลย

     ☐ 2) นานๆ ครั้ง

     ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่งของการถ่ายอุจจาระ)

     ☐ 4) บ่อยครั้ง (มากกว่าครึ่งของการถ่ายอุจจาระ)

     ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

5. มีความรู้สึกเหมือนถ่ายอุจจาระไม่สุดหลังการถ่ายอุจจาระแต่ละครั้ง บ่อยครั้งแค่ไหน

     ☐ 1) ไม่มีอาการเลย

     ☐ 2) นานๆ ครั้ง

     ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่งของการถ่ายอุจจาระ)

     ☐ 4) บ่อยครั้ง (มากกว่าครึ่งของการถ่ายอุจจาระ)

     ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

6. ต้องใช้นิ้วช่วยล้วงหรือสวนอุจจาระ ขณะถ่ายอุจจาระบ่อยครั้งแค่ไหน

     ☐ 1) ไม่มีอาการเลย

     ☐ 2) นานๆ ครั้ง

     ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่งของการถ่ายอุจจาระ)

     ☐ 4) บ่อยครั้ง (มากกว่าครึ่งของการถ่ายอุจจาระ)

     ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

7. โดยปกติใช้เวลานานแค่ไหนในการถ่ายอุจจาระแต่ละครั้ง

     ☐ 1) น้อยกว่า 5 นาที

     ☐ 2) 5- น้อยกว่า 10 นาที

     ☐ 3) 10- น้อยกว่า 15 นาที

     ☐ 4) 15- น้อยกว่า 20 นาที

     ☐ 5) มากกว่า 20 นาที

8. ขณะที่ถ่ายอุจจาระมีอาการเหล่านี้ร่วมด้วยหรือไม่ (ตอบได้มากกว่า 1 ข้อ)

     ☐ 1) ปวดท้อง

     ☐ 2) ผายลม

     ☐ 3) มีปัสสาวะกระปริดกระปรอย

     ☐ 4) มีแสบหรือเจ็บที่รูทวารหนัก

     ☐ 5) มีเลือดออกปนออกมากับอุจจาระ

9. ในขณะที่รู้สึกปวดอยากถ่ายอุจจาระมีการกลั้นอุจจาระบ่อยแค่ไหน

    ☐ 1) ไม่เคยกลั้นอุจจาระเลย

    ☐ 2) นานๆ ครั้ง

    ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่ง)

    ☐ 4) บ่อยครั้ง (มากกว่าครึ่ง)

    ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

10. ในขณะที่ถ่ายอุจจาระมีการทำกิจกรรมเช่น อ่านหนังสือ/การ์ตูน หรือดูโทรทัศน์บ่อยแค่ไหน

    ☐ 1) ไม่เคย

    ☐ 2) นานๆ ครั้ง

    ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่ง)

    ☐ 4) บ่อยครั้ง (มากกว่าครึ่ง)

    ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

ส่วนที่ 4.2 ข้อมูลกับแบบแผนการถ่ายอุจจาระ 1 เดือน ก่อนเข้าร่วมการวิจัย

1. ในระยะเวลา 3 เดือนที่ผ่านมา มีการถ่ายอุจจาระบ่อยมากแค่ไหน

    ☐ 1) มากกว่า 2 ครั้งต่อวัน

    ☐ 2) 1-2 ครั้งต่อวัน

    ☐ 3) 4-6 ครั้งต่อสัปดาห์ (เกือบทุกวัน)

    ☐ 4) 3 ครั้งต่อสัปดาห์ (วันเว้นวัน)

    ☐ 5) น้อยกว่า 3 ครั้งต่อสัปดาห์

2. ส่วนใหญ่อุจจาระมีลักษณะอย่างไร

    ☐ 1) ก้อนนิ่มไม่เป็นลำ/เหลว/คล้ายโคลน

    ☐ 2) ลำยาวอ่อนนุ่ม

    ☐ 3) ลำยาวคล้ายไส้กรอก

    ☐ 4) ลำยาวแข็ง

    ☐ 5) ก้อนแข็ง ไม่เป็นลำ คล้ายขี้แพะหรือเม็ดถั่ว

3. เด็กต้องออกแรงเบ่งมากกว่าปกติ ขณะถ่ายอุจจาระบ่อยครั้งแค่ไหน

    ☐ 1) ไม่ต้องเบ่งเลย

    ☐ 2) นานครั้ง

    ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่งของการถ่ายอุจจาระ)

    ☐ 4) บ่อยครั้ง (มากกว่าครึ่งของการถ่ายอุจจาระ)

    ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

4. มีอาการปวดก้น (รูทวารหนัก) ขณะถ่ายอุจจาระบ่อยครั้งแค่ไหน

    ☐ 1) ไม่มีอาการเลย

    ☐ 2) นานๆ ครั้ง

    ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่งของการถ่ายอุจจาระ)

    ☐ 4) บ่อยครั้ง (มากกว่าครึ่งของการถ่ายอุจจาระ)

    ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

5. มีความรู้สึกเหมือนถ่ายอุจจาระไม่สุดหลังการถ่ายอุจจาระแต่ละครั้ง บ่อยครั้งแค่ไหน

    ☐ 1) ไม่มีอาการเลย

    ☐ 2) นานๆ ครั้ง

    ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่งของการถ่ายอุจจาระ)

    ☐ 4) บ่อยครั้ง (มากกว่าครึ่งของการถ่ายอุจจาระ)

    ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

6. ต้องใช้นิ้วช่วยล้วงหรือสวนอุจจาระ ขณะถ่ายอุจจาระบ่อยครั้งแค่ไหน

    ☐ 1) ไม่มีอาการเลย

    ☐ 2) นานๆ ครั้ง

    ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่งของการถ่ายอุจจาระ)

    ☐ 4) บ่อยครั้ง (มากกว่าครึ่งของการถ่ายอุจจาระ)

    ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

7. โดยปกติใช้เวลานานแค่ไหนในการถ่ายอุจจาระแต่ละครั้ง

    ☐ 1) น้อยกว่า 5 นาที

    ☐ 2) 5- น้อยกว่า 10 นาที

    ☐ 3) 10- น้อยกว่า 15 นาที

    ☐ 4) 15- น้อยกว่า 20 นาที

    ☐ 5) มากกว่า 20 นาที

8. ขณะที่ถ่ายอุจจาระมีอาการเหล่านี้ร่วมด้วยหรือไม่ (ตอบได้มากกว่า 1 ข้อ)

    ☐ 1) ปวดท้อง

    ☐ 2) ผายลม

    ☐ 3) มีปัสสาวะกระปริดกระปรอย

    ☐ 4) มีแสบหรือเจ็บที่รูทวารหนัก

    ☐ 5) มีเลือดออกปนออกมากับอุจจาระ

9. ในขณะที่รู้สึกปวดอยากถ่ายอุจจาระมีการกลั้นอุจจาระบ่อยแค่ไหน

    ☐ 1) ไม่เคยกลั้นอุจจาระเลย

    ☐ 2) นานๆ ครั้ง

    ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่ง)

    ☐ 4) บ่อยครั้ง (มากกว่าครึ่ง)

    ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

10. ในขณะที่ถ่ายอุจจาระมีการทำกิจกรรมเช่น อ่านหนังสือ/การ์ตูน หรือดูโทรทัศน์บ่อยแค่ไหน

    ☐ 1) ไม่เคย

    ☐ 2) นานๆ ครั้ง

    ☐ 3) เป็นบางครั้ง (ประมาณครึ่งหนึ่ง)

    ☐ 4) บ่อยครั้ง (มากกว่าครึ่ง)

    ☐ 5) เกือบทุกครั้ง/ทุกครั้ง

11. ลักษณะของอุจจาระครั้งสุดท้าย

ความแข็ง :	☐ 1) แข็ง	☐ 2) ปกติ	☐ 3) อ่อน	☐ 4) เหลว
สี :	☐ 1) ดำ	☐ 2) น้ำตาลเข้ม	☐ 3) น้ำตาล	☐ 4) น้ำตาลอ่อน
ปริมาณ :	☐ 1) เล็กน้อย	☐ 2) ปานกลาง	☐ 3) มาก	
กลิ่น :	☐ 1) ไม่มี	☐ 2) มี		
มีเลือดปน :	☐ 1) ไม่มี	☐ 2) มี		

แบบบันทึกการถ่ายอุจจาระและอาการข้างเคียงขณะเข้าร่วมการวิจัย

การถ่ายอุจจาระขณะเข้าร่วมการวิจัย

สัปดาห์ที่ .... วันที่ .... ถึงวันที่ ....

วัน/เดือน/ปี	การถ่ายอุจจาระ		ลักษณะของอุจจาระ				ลักษณะการเบ่ง		หมายเหตุ
	ถ่าย	ไม่ถ่าย	เหลวเป็นน้ำ (ชนิด 7)	ก้อนนิ่มเหลว (ชนิด 5-6)	ปกติ (ชนิด4)	ก้อนแข็ง (ชนิด1-3)	ปกติ	มากกว่าปกติ	

อาการข้างเคียงขณะเข้าร่วมการวิจัย

สัปดาห์ที่ .... วันที่ .... ถึงวันที่ ....

1. ช่วงระหว่างการศึกษาท่านมีอาการเจ็บป่วยหรือไม่ ☐ ไม่มี ☐ มี (โปรดระบุ).................

2. ท่านสังเกตพบว่ามีอาการต่างๆ เหล่านี้เกิดขึ้นในระหว่างการได้รับยาหรือไม่ (ตอบได้ > 1 ข้อ)

   ☐ 1) คลื่นไส้   ☐ 2) อาเจียน
   ☐ 3) ปวดศรีษะ/วิงเวียน   ☐ 4) ไม่รู้สึกอยากอาหาร
   ☐ 5) ผายลมบ่อยครั้งหรือจำนวนมาก ☐ 6) รู้สึกไม่สบายท้อง แน่นท้อง
   ☐ 7) ท้องอืด   ☐ 8) ปวดท้อง
   ☐ 9) ท้องเสีย   ☐ 10) อื่นๆ ....

3. อาการที่เกิดขึ้นจากข้อ 2 เป็นมากน้อยเท่าใด (ระดับ 1-5 โดยที่ 1 น้อยที่สุดและ 5 มากที่สุด)

   ระดับ ☐ 1   ☐ 2   ☐ 3   ☐ 4   ☐ 5

4. ความถี่ของอาการที่เกิดขึ้นจากการได้รับยาในแต่ละสัปดาห์

   ☐ 1) ไม่มีอาการ   ☐ 2) 1-2 ครั้ง
   ☐ 3) 3-4 ครั้ง   ☐ 4) 5-6 ครั้ง
   ☐ 5) ทุกวัน

วิธีการแก้ไข..

วิธีการบันทึกการถ่ายอุจจาระ (ควรบันทึกทันทีหลังจากถ่ายอุจจาระทุกครั้ง)

1. วันที่บันทึก :

   ทำการบันทึกทุกวันทั้งในสถานะการณ์ที่ไม่มีและมีการถ่ายอุจจาระในแต่ละสัปดาห์ เช่น
   สัปดาห์ที่ 1 ตั้งแต่วันที่ 1 ก.ค. 50 ถึงวันที่ 7 ก.ค. 50 ซึ่งให้บันทึกทั้ง 7 วันลงในตาราง

2. การถ่ายอุจจาระ :

   ทำการบันทึกในช่อง "ถ่าย"   =   เมื่อมีการถ่ายอุจจาระ

   　　　　　　　　　　"ไม่ถ่าย"   =   เมื่อไม่มีการถ่ายอุจจาระ

3. ลักษณะของอุจจาระ:

   บันทึกลักษณะของอุจจาระที่ได้โดยเปรียบเทียบกับรูปที่แนบมาให้ (รูปลักษณะอุจจาระ
   จาก The Bristol Stool Form Scale โดยจะแบ่งเป็น 4 กลุ่ม คือ

   3.1) เหลวเป็นน้ำ : ลักษณะของอุจจาระที่ไม่เป็นก้อน (ชนิดที่ 7)

   3.2) ก้อนนิ่มเหลว : ลักษณะของอุจจาระที่ก้อนนิ่มเล็ก ซึ่งมีรูปร่างไม่แน่นอน แต่ไม่จับตัว
   　　　เป็นก้อนแน่น (ชนิดที่ 5-6)

   3.3) ปกติ : ลักษณะของอุจจาระที่เป็นรูปไส้กรอกเรียวยาว และพื้นผิวเรียบไม่มีรอยแตก
   　　　(ชนิดที่ 4)

   3.4) ก้อนแข็ง : ลักษณะอุจจาระที่เป็นรูปไส้กรอกที่มีรอยแตกที่พื้นผิวหรือเป็นก้อนเล็ก
   　　　แข็งที่เกาะกันเป็นก้อนหรือเป็นก้อนเล็กแข็ง (ชนิดที่ 1-3)

4. ลักษณะการเบ่ง :

   บันทึกแรงเบ่งที่ใช้ในขณะการถ่ายอุจจาระในช่อง

   　　　"ปกติ"   =   ไม่ต้องใช้แรงเบ่งจนถึงแรงเบ่งการถ่ายอุจจาระปกติ

   　　　"มากกว่าปกติ" =   ต้องใช้แรงเบ่งมากว่าปกติ

5. อื่นๆ :

   บันทึกข้อมูลอื่นๆ ที่มีความผิดปกติในขณะถ่ายอุจจาระในช่อง "หมายเหตุ" เช่น ความรู้สึก
   ถ่ายอุจจาระไม่สุดหลังถ่ายอุจจาระ หรือมีอาการปวดแสบรูทวารหนักขณะถ่ายอุจจาระ
   หรืออุจจาระมีเลือดปนออกมา เป็นต้น

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces ENTIRELY LIQUID

ภาพแสดง: ลักษณะของอุจจาระจาก The Bristol Stool Form Scale (Candy และ Edwards, 2003)

แบบบันทึกการบริโภคอาหาร 24 ชั่วโมง ก่อนเริ่มทำการวิจัย

<u>บันทึกก่อนเริ่มทำการวิจัย</u>

รายการอาหารที่รับประทาน ในวันที่............... เดือน...พ.ศ.......................

มื้อ อาหาร/ เวลา	สถานที่ รับประทาน อาหาร	ส่วนประกอบ ของอาหาร	ปริมาณที่ รับประทาน	วิธีการปรุง อาหาร	เครื่องดื่ม	ปริมาณที่ รับประทาน

แบบบันทึกการบริโภคอาหาร 3 วัน ขณะเข้าร่วมการวิจัย

<u>บันทึกวันที่ 1</u>

รายการอาหารที่รับประทาน ในวันที่............... เดือน...พ.ศ........................

มื้อ อาหาร/ เวลา	สถานที่ รับประทาน อาหาร	ส่วนประกอบ ของอาหาร	ปริมาณที่ รับประทาน	วิธีการปรุง อาหาร	เครื่องดื่ม	ปริมาณที่ รับประทาน

<u>บันทึกวันที่ 2</u>

รายการอาหารที่รับประทาน ในวันที่............... เดือน...พ.ศ.......................

มื้อ อาหาร/ เวลา	สถานที่ รับประทาน อาหาร	ส่วนประกอบ ของอาหาร	ปริมาณที่ รับประทาน	วิธีการปรุง อาหาร	เครื่องดื่ม	ปริมาณที่ รับประทาน

<u>บันทึกวันที่ 3</u>

รายการอาหารที่รับประทาน ในวันที่............... เดือน...พ.ศ.......................

มื้อ อาหาร/ เวลา	สถานที่ รับประทาน อาหาร	ส่วนประกอบ ของอาหาร	ปริมาณที่ รับประทาน	วิธีการปรุง อาหาร	เครื่องดื่ม	ปริมาณที่ รับประทาน

วิธีการบันทึกการบริโภคอาหาร 3 วัน

วันที่ควรจดบันทึกการรับประทานอาหารนั้นควรประกอบด้วย วันธรรมดา (จันทร์-ศุกร์) 2 วันและ วันหยุด (เสาร์-อาทิตย์) 1 วัน เป็นเวลา 3 วัน

ทำการบันทึกการรับประทานอาหารและเครื่องดื่มทุกมื้อ ตั้งแต่เช้าจนเข้านอนและควรทำการบันทึก ทันทีขณะหรือหลังรับประทาน

ข้อมูลที่สำคัญของการจดบันทึกการบริโภคอาหาร 3 วัน ประกอบด้วย

1. ชนิดของมื้ออาหาร :
   บันทึกมื้ออาหารที่รับประทานพร้อมทั้งระบุเวลาที่รับประทานโดยประมาณ
   เช่น เช้า-กลางวัน-เย็น-อาหารว่าง

2. รายการอาหารและเครื่องดื่ม :
   บันทึกรายการอาหาร รวมทั้งเครื่องดื่มทุกชนิดที่รับประทานตั้งแต่ผู้ป่วยตื่นนอน
   จนกระทั่งเข้านอนต่อเนื่องกัน 3 วัน
   เช่น ข้าวต้มปลา ก๋วยเตี๋ยวเส้นเล็กลูกชิ้นปลา น้ำมะตูม เป็นต้น

3. ส่วนประกอบ :
   บันทึกส่วนประกอบต่างๆ ของอาหารและเครื่องดื่มที่รับประทาน
   เช่น ข้าวต้มปลา มีส่วนประกอบด้วย ข้าว เนื้อปลา ผักชี หัวหอม

4. ปริมาณที่รับประทาน :
   ระบุปริมาณอาหารและเครื่องดื่มที่รับประทานโดยประมาณ เช่น ข้าวต้มปลา ประกอบด้วย
   ข้าว 1   ถ้วยตวง เนื้อปลา 2 ช้อนโต๊ะ โดยกำหนดปริมาณอาหารและเครื่องดื่ม เช่น

1 ถ้วยตวง	=	240 มิลลิลิตร
1 ช้อนชา	=	5 มิลลิลิตร
2 ช้อนโต๊ะ	=	30 กรัม
1 ช้อนโต๊ะ	=	15 มิลลิลิตร
3 ช้อนชา	=	1 ช้อนโต๊ะ
16 ช้อนโต๊ะ	=	1 ถ้วยตวง

5. วิธีการเตรียมหรือวิธีการปรุงอาหารเครื่องดื่ม :
   ระบุวิธีการประกอบอาหารและเครื่องดื่มที่รับประทาน ตัวอย่างเช่น ต้ม ตุ๋น ผัด ทอด ลวก
   ปิ้ง ย่าง แกง แช่แข็ง รับประทานสด อาหารกระป๋อง

6. สถานที่รับประทานอาหารและเครื่องดื่ม :
   ระบุสถานที่รับประทานอาหารและเครื่องดื่ม เช่น บ้าน ที่โรงเรียน ร้านอาหาร

7. ผลิตภัณฑ์เสริมอาหาร :
   ระบุผลิตภัณฑ์เสริมอาหารที่รับประทาน เช่น วิตามิน แร่ธาตุ พร้อมทั้งระบุจำนวน และ
   วิธีการรับประทาน

Appendix C

- **Approval of certificate from Queen Sirikit Institute of Child Health**

- **Information sheet for participants**

- **Consent form**

EC.013/2550

คณะกรรมการพิจารณาการศึกษาวิจัยในมนุษย์
ของสถาบันสุขภาพเด็กแห่งชาติมหาราชินี

17 ตุลาคม 2550

โครงการวิจัย : ผลของฟรักโทโอลิโกแซ็กคาไรด์ต่อภาวะท้องผูกในผู้ป่วยเด็ก ณ สถาบันสุขภาพเด็กแห่งชาติ

มหาราชินี : Effect of Fructooligosaccharide on Constipation in Pediatric Patients at

Queen Sirikit National Institute of Child Health

ผู้ดำเนินการวิจัย : เภสัชกรหญิงพัชรินทร์ วิจิตรเวียงรัตน์ และ แพทย์หญิงนิยะดา วิทยาศัย

สถานที่ดำเนินการวิจัย : สถาบันสุขภาพเด็กแห่งชาติมหาราชินี

เอกสารที่พิจารณา :

1. แบบเสนอโครงการวิจัยเพื่อขอรับการพิจารณาจากคณะกรรมการพิจารณาการศึกษาวิจัยในมนุษย์

   ของสถาบันสุขภาพเด็กแห่งชาติมหาราชินี (ภาษาไทย ฉบับแก้ไขวันที่ 16 ตุลาคม2550)

2. แบบบันทึกข้อมูลงานวิจัย(CRF)

3. แบบสอบถามผู้เข้าร่วมโครงการวิจัย(Questionnaire)

4. เอกสารแนะนำอาสาสมัคร,ใบยินยอมด้วยความสมัครใจในการเข้าร่วมโครงการวิจัย และ ใบยินยอม

   ด้วยความสมัครใจในการเข้าร่วมโครงการวิจัย(กรณีผู้ป่วยอายุ 7-12 ปี)

คณะกรรมการพิจารณาการศึกษาวิจัยในมนุษย์ของสถาบันสุขภาพเด็กแห่งชาติมหาราชินี ได้พิจารณา
โครงการฉบับภาษาไทย ฉบับแก้ไข วันที่ 16 ตุลาคม 2550 แล้ว คณะกรรมการฯ พิจารณาอนุมัติในแง่จริยธรรม
ให้ดำเนินการศึกษาวิจัยเรื่องข้างต้นได้ ตั้งแต่ วันที่ 17 ตุลาคม 2550 ถึงวันที่ 16 ตุลาคม 2551 อนึ่ง ท่านต้อง
รายงานสถานะของโครงการให้คณะกรรมการฯ ทราบทุกปี เพื่ออนุมัติดำเนินโครงการต่อ จนกว่าจะหมดอายุ
โครงการ

....

(นางสาวศศิชล คำเพราะ)

กรรมการและเลขานุการคณะกรรมการพิจารณาการศึกษาวิจัยในมนุษย์

ของสถาบันสุขภาพเด็กแห่งชาติมหาราชินี

....

(รศ.พิเศษ นายแพทย์ทวี โชติพิทยสุนนท์)

ประธานคณะกรรมการพิจารณาการศึกษาวิจัยในมนุษย์

ของสถาบันสุขภาพเด็กแห่งชาติมหาราชินี

วันที่ประชุม 8 ตุลาคม 2550

รับรองตั้งแต่วันที่ 17 ตุลาคม 2550 **ถึงวันที่** 16 ตุลาคม 2551

ข้อมูลคำอธิบาย/ชี้แจงแก่ผู้เข้าร่วมวิจัย

1. ชื่อโครงการวิจัย "ผลของฟรักโทโอลิโกแซ็กคาไรด์ต่อภาวะท้องผูกในผู้ป่วยเด็ก ณ สถาบัน สุขภาพเด็กแห่งชาติมหาราชินี"

2. ชื่อผู้วิจัย นางสาวพัชรินทร์ วิจิตรเวียงรัตน์

   ศึกษาต่อปริญญาโท ที่คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

3. สถานที่ติดต่อ ภาควิชาอาหารเคมี คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

   หมายเลขโทรศัพท์ 02-2188291-5 โทรสาร 02-2188296 โทรศัพท์เคลื่อนที่ 085-1225858 สามารถติดต่อได้ตลอด 24 ชั่วโมง และถ้ามีปัญหาเกี่ยวกับสิทธิของผู้ป่วยหรือความไม่ชอบ ธรรมของงานวิจัยสามารถติดต่อได้ที่ เลขานุการคณะกรรมการพิจารณาการศึกษาวิจัยในมนุษย์ ของสถาบันสุขภาพเด็กแห่งชาติมหาราชินี ศูนย์วิจัยและพัฒนา อาคารสถาบันสุขภาพเด็ก แห่งชาติมหาราชินี ชั้น 12 โทรศัพท์/โทรสาร 02-6448943 เบอร์โทรศัพท์ภายใน 02-3548333 ถึง 43 ต่อ 5210, 5211

4. เนื้อหาสาระโครงการวิจัยและความเกี่ยวข้องกับอาสาสมัคร ได้แก่

   4.1 เหตุผลและความจำเป็นที่ต้องทำการศึกษาวิจัย เนื่องจากในปัจจุบันพบว่า ผู้ป่วยเด็กมี ปัญหาจากภาวะท้องผูกเพิ่มมากขึ้น โดยสัดส่วนของเด็กที่มีปัญหาท้องผูกจะมี แนวโน้มเพิ่มขึ้นในแต่ละปี โดยภาวะท้องผูกขึ้นอยู่กับแต่ละบุคคล อาการที่เกิดขึ้นคือ มีอาการถ่ายอุจจาระลำบาก อุจจาระได้ไม่สุดหรือลักษณะของอุจจาระที่แข็งกว่าปกติ นอกจากนี้อาจยังพบอาการอื่นๆ ร่วมด้วย เช่น ปวดท้อง คลื่นไส้ อาเจียน ท้องอืด และ อุจจาระถ่ายเป็นเลือด ซึ่งเป็นผลเสียต่อสุขภาพของเด็ก

   4.2 วัตถุประสงค์ของการศึกษาวิจัย

   — ผลของการเสริมฟรักโทโอลิโกแซ็กคาไรด์ต่อจำนวนครั้งของการถ่ายอุจจาระ ต่อสัปดาห์, ลักษณะของอุจจาระและลักษณะอาการที่เกิดขึ้นในขณะถ่าย อุจจาระของผู้ป่วยเด็กท้องผูกเรื้อรัง

   — ผลข้างเคียงของฟรักโทโอลิโกแซ็กคาไรด์ในผู้ป่วยเด็กที่มีภาวะท้องผูกที่อาจ เกิดขึ้นระหว่างการวิจัย เช่น อาการแน่นท้อง ปวดท้อง ท้องอืด และท้องเสีย เป็นต้น

   4.3 ข้อมูลของใยอาหารที่ชื่อฟรักโทโอลิโกแซ็กคาไรด์ เป็นกลุ่มของใยอาหารที่สามารถ พบได้ในผักและผลไม้ทั่วไป โดยมีบทบาททางด้านอาหารและโภชนาการ ซึ่งไม่ สามารถย่อยและดูดซึมได้ในลำไส้เล็ก ทำให้มีฤทธิ์ในการเป็นยาระบายได้ รวมทั้งยัง ส่งผลให้ยับยั้งการเจริญเติบโตของแบคทีเรียที่ก่อโรค แต่กระตุ้นการเจริญเติบโตของ พวกแบคทีเรียที่ดีในลำไส้ แต่มีรายงานอาการข้างเคียงที่เกิดขึ้นจากการรับประทานใย

อาหารพบว่าทำให้เกิดท้องอืดหรือแน่นท้องได้ ซึ่งพบได้น้อยมาก ส่วนมิลค์อ็อฟแมกนี
เซียเป็นยาระบายที่มีคุณสมบัติในการดูดซึมได้น้อย ทำให้เพิ่มแรงดันในโพรงลำไส้
ใหญ่กระตุ้นการถ่ายอุจจาระ สามารถนำมาใช้ในผู้ป่วยท้องผูกเรื้อรังได้ แต่อาจเป็นพิษ
ได้ในผู้ป่วยโรคไต ซึ่งพบได้น้อยมากเช่นกัน

4.4 วิธีการศึกษาวิจัยโดยสังเขป ผู้ป่วยเด็กท้องผูกเรื้อรังที่ได้รับการวินิจฉัยจากแพทย์แล้ว
จะแบ่งเป็นสองกลุ่ม โดยกลุ่มที่หนึ่งเป็นการรักษาด้วยยามิลค์อ็อฟแมกนีเซีย (กลุ่ม
มาตรฐาน) ซึ่งผู้ป่วยต้องชำระเงินเองในราคาขวดละ 7 บาท และกลุ่มที่สองได้รับใย
อาหารที่ชื่อฟรักโทโอลิโกแซ็กคาไรด์ (กลุ่มทดลอง) ซึ่งผู้ป่วยจะได้รับจากผู้วิจัยโดย
ไม่ต้องชำระเงิน เป็นระยะเวลา 30 วัน โดยมีการเก็บข้อมูลของผู้ป่วยในช่วงก่อน
ระหว่าง และหลังการวิจัย ในรายละเอียดของความถี่ ลักษณะอุจจาระ อาการที่เกิดขึ้น
ในขณะถ่ายอุจจาระ ผลข้างเคียง การเจริญเติบโตของเด็ก และการบันทึกรายการ
อาหารที่รับประทาน เพื่อนำข้อมูลไปประเมินผลเปรียบเทียบทางสถิติ

4.5 ระยะเวลาที่อาสาสมัครต้องเกี่ยวข้องในการศึกษาวิจัย ตั้งแต่การรับเข้าการวินิจฉัยว่า
เป็นท้องผูกเรื้อรัง จนกระทั่งหลังจากการหยุดได้รับการรักษาเป็นระยะเวลา 14 วัน

4.6 เอกสารที่ผู้ป่วยจะต้องบันทึกในระหว่างทำการวิจัย คือ บันทึกการบริโภคอาหาร 3 วัน,
การถ่ายอุจจาระ, ลักษณะอุจจาระ และอาการข้างเคียง (ภาคผนวก ข)

4.7 ประโยชน์ที่คาดว่าจะเกิดขึ้นทั้งต่ออาสาสมัครและต่อผู้อื่น

 — นำข้อมูลที่ได้ไปใช้เป็นแนวทางในการพิจารณาเสริมฟรักโทโอลิโกแซ็กคา
 ไรด์ในผู้ป่วยเด็กที่มีอาการท้องผูกเรื้อรังในปริมาณที่เหมาะสมต่อเด็กโดยไม่
 ก่อให้เกิดผลข้างเคียงในเด็ก

 — เพื่อเป็นข้อมูลในการแนะนำพฤติกรรมการบริโภค และกิจกรรมประจำวัน
 สำหรับผู้ป่วยเด็กที่มีอาการท้องผูกเรื้อรัง

4.8 ขอบเขตการดูแลรักษาความลับของข้อมูลต่างๆ ของอาสาสมัคร ผู้วิจัยจะเก็บข้อมูลทุก
อย่างเป็นความลับเฉพาะแต่ละอาสาสมัคร แต่จะมีการเปิดเผยข้อมูลในรูปแบบรายงาน
การวิจัยเป็นภาพรวม โดยไม่มีการระบุข้อมูลของแต่ละอาสาสมัคร

4.9 กรณีเกิดอันตรายหรือผลไม่พึงประสงค์จากการศึกษาวิจัย อาสาสมัครจะได้รับการดูแล
รักษาโดยไม่ต้องเสียค่าใช้จ่ายอย่างไรบ้าง

 — เมื่อผู้ป่วยมีอาการข้างเคียงจากการได้รับยา ผู้ป่วยจะได้รับการรักษาตามอาการที่
 เกิดขึ้นโดยไม่เสียค่าใช้จ่าย เช่น อาการท้องอืดจะได้รับยาขับลม เป็นต้น

4.10 การตอบแทนชดเชยแก่อาสาสมัคร โดยระบุจำนวนและกำหนดเวลาทนแทนชดเชย
อย่างชัดเจน

— ผู้ป่วยจะได้รับค่าชดเชยเสียเวลาจากการเข้าร่วมการวิจัยคนละ 100 บาทต่อ ครั้งที่มาพบตามนัด (คนละ 2 ครั้งคือ หลังจากหยุดได้รับและช่วงที่ไม่ได้รับ 14 วัน)

4.11 การถอนตัวออกจากโครงการวิจัย อาสาสมัครสามารถถอนตัวออกจากโครงการวิจัย ได้ทุกเมื่อ โดยไม่กระทบต่อการดูแลรักษาที่พึงได้รับตามปกติ

4.12 ชื่อ ที่อยู่ เบอร์โทรศัพท์ของผู้วิจัยที่อาสาสมัครสามารถติดต่อได้ ตามข้อความใน เอกสารข้อ 2 และ 3

ใบยินยอมด้วยความสมัครใจในการเข้าร่วมวิจัย

โครงการวิจัยเรื่อง ผลของฟรักโทโอลิโกแซ็กคาไรด์ต่อภาวะท้องผูกในผู้ป่วยเด็ก ณ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี

วันที่ให้คำยินยอม วันที่........................... เดือน............................. พ.ศ. ....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึง วัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตรายหรืออาการที่อาจจะเกิดขึ้นจากการวิจัยหรือยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด และมีความเข้าใจดีแล้ว

ผู้วิจัยรับรองว่าจะตอบคำถามต่างๆ ที่ข้าพเจ้าสงสัยด้วยความเต็มใจ ไม่ปิดบัง ซ่อนเร้นจน ข้าพเจ้าพอใจ

ข้าพเจ้ามีสิทธิ์ที่จะบอกเลิกการเข้าร่วมในโครงการวิจัยนี้เมื่อใดก็ได้ และเข้าร่วม โครงการวิจัยนี้โดยสมัครใจและการบอกเลิกการเข้าร่วมการวิจัย จะไม่มีผลต่อการรักษาโรคที่บุตร หรือเด็กในปกครองของข้าพเจ้าจะได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะเกี่ยวกับบุตรหรือเด็กในปกครองของข้าพเจ้าเป็น ความลับและเปิดเผยได้เฉพาะในรูปที่เป็นสรุปผลการวิจัย หรือการเปิดเผยข้อมูลต่อผู้มีหน้าที่ที่ เกี่ยวข้องกับการสนับสนุนและกำกับดูแลการวิจัย

ข้าพเจ้าสามารถติดต่อได้ที่ นางสาวพัชรินทร์ วิจิตรเวียงรัตน์ บ้านเลขที่ 1581 ถนนริมทาง รถไฟสายปากน้ำ แขวงคลองตัน เขตคลองเตย กรุงเทพมหานคร และหมายเลขโทรศัพท์ 085-1225858 ซึ่งเป็นผู้รับผิดชอบงานวิจัยนี้ และถ้ามีปัญหาเกี่ยวกับสิทธิของผู้ป่วยหรือความไม่ชอบ ธรรมของงานวิจัยสามารถติดต่อได้ที่ เลขานุการคณะกรรมการพิจารณาการศึกษาวิจัยในมนุษย์ของ สถาบันสุขภาพเด็กแห่งชาติมหาราชินี ศูนย์วิจัยและพัฒนา อาคารสถาบันสุขภาพเด็กแห่งชาติมหา ราชินี ชั้น 12 โทรศัพท์/โทรสาร 02-6448943 เบอร์โทรศัพท์ภายใน 02-3548333 ถึง 43 ต่อ 5210, 5211

ข้าพเจ้าได้อ่านข้อความข้างต้นแล้ว และมีความเข้าใจดีทุกประการ และได้ลงนามในใบ ยินยอมนี้ด้วยความเต็มใจ

ในกรณีผู้ถูกทดลองยังไม่บรรลุนิติภาวะจะต้องได้รับการยินยอมจากผู้ปกครองหรือผู้ อุปการะโดยชอบด้วยกฎหมาย

ลงนาม .... มารดา/บิดา
กรณีที่ผู้ปกครองไม่ใช่มารดา/บิดา มีความสัมพันธ์เป็น ....กับผู้ป่วย
ลงนาม .... ผู้ปกครอง
ลงนาม .... พยาน

ลงนาม .... พยาน
ลงนาม .... ผู้วิจัย

ใบยินยอมด้วยความสมัครใจในการเข้าร่วมวิจัย (กรณีผู้ป่วยอายุ 7-12 ปี)

รายละเอียดการวิจัย

วันที่ 1

 +

บันทึกข้อมูลการบริโภค
อาหารและการถ่ายอุจจาระ

วันที่ 14

มาที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี พบ
คุณหมอดูอาการว่าอาการท้องผูกเป็นอย่างไร

บันทึกข้อมูลการบริโภค
อาหารและการถ่ายอุจจาระ

วันที่ 44

มาที่สถาบันสุขภาพเด็กแห่งชาติมหาราชินี พบ
คุณหมอดูอาการว่าอาการท้องผูกเป็นอย่างไร

ให้กากบาทในช่อง ☐

สนใจเข้าร่วม 😊   ไม่สนใจเข้าร่วม 😠

☐   ☐

Appendix D

FOS formulation

Fructooligosaccharide preparation was formulated for this study so as to have suitable concentration and stability, as well as to be appropriate for children.

1.   Preparation of fructooligosaccharide solution (Winfield, 2004)

1.1   Solubility of fructooligosaccharides

An appropriate concentration of FOS was determined. Several trials on the proportions of FOS and distilled water 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9 and 1:10 w/v were performed. The temperature of distilled water varied at 10, 28 and 60° C. The most suitable proportion was selected to use in the next step.

1.2   Formulation of fructooligosaccharide solution

The best concentration of FOS from 1.1 was selected and added with other ingredients to improve the palatability and appearance of the formulation. These ingredients included sweentening agents, preservatives, flavoring agents, and coloring agents. Vehicle of this preparation was distilled water because FOS can dissolve in water, commonly used in oral preparations.

1.2.1   *Sweentening agent* in this experiment was glucose as it gives a pleasant texture in the mouth. Although prolonged use of liquid medicine containing glucose can lead to an increased incidence of dental caries, particularly in children, it is still common to use glucose in pediatric formulation. The concentration of glucose used in this formulation was not higher than 15% w/v following recommendation of the Department of Health that supports the low sugar intake in the children. In this experiment various concentrations of glucose were tried (2, 4, 7, 10 and 15%). The taste of the product was evaluated by 10 volunteers and the best formula was chosen for use in the next step

1.2.2   *Preservatives* are usually used in most water-containing formulas, to reduce or prevent microbial growth. Parabens was used as preservative

in the formula because of its effectiveness over a wide range of pH (4-8) and broad spectrum of antimicrobial activity including yeasts and molds. Parabens is a combination of methylparaben and propylparaben in the ratio of 5:1 mixed in propylene glycol. Parabens in concentration of 1% was used in the formula (Rowe et al, 2006).

1.2.3 *Flavoring agents* added to the preparation can make it more acceptable to take. The age of the patients should be taken into account when selecting a flavor. The children tend to enjoy fruit or sweet flavors. Thus, the flavor used in the formulation included banana, orange, strawberry and apple flavors.

1.2.4 *Coloring agents* are added to the preparation to enhance the appearance or increase the acceptability of the preparation. The selected colors and flavors should be matched. In the experiment, yellow color was used for a banana-flavored, orange color for an orange-flavored, red color for a strawberry-flavored, and green color for an apple-flavored preparations.

1.3 Stability of fructooligosaccharide preparation

The suitable formula was kept to be observed its stability. The physical properties were observed at 0, 14, 30, 60, 90, and 120 days, and the microbiological test was performed at 30, 60, 90, and 120 days.

1.3.1 Physical properties of the formula included color, turbidity, odor, flavor, and pH.

1.3.2 Microbiological test for nonsterile product, is suggested that oral solutions and suspensions should be tested routinely for *Escherichia coli* and *Salmonella spp* (USP, 2005) by method from Department of Health, Ministry of Public Health, Thailand. The media solutions called ว.810 and ว.111 were used for determination of *Salmonella spp.* and coliform bacteria (*Escherichia coli*)

respectively. The test kits were purchased from Department of Health, Ministry of Public Health. Aseptic technique was performed. Distilled water and tap water were used as negative and positive controls respectively. Test solutions were drawn and added into media solutions at the label limit and then close the cap and mix solution together. All media were incubated at 37° C for 24-48 hours and compare with calibrated color chart.

      1.4   Evaluation of satisfaction

The formula which passed the microbiological test was evaluated for satisfaction in 40 children aged 4-12 years. The color, flavor and total appearance of the formula were evaluated by a 5-point scale of liking that ranged from "Like extremely" to "Dislike extremely" (Figure D-1).

แบบประเมินความพึงพอใจของผลิตภัณฑ์

1. ลักษณะภายนอกของผลิตภัณฑ์

1.1 สีของผลิตภัณฑ์ (ความชอบน้อยไปมาก, 1-5)

สูตรตำรับ	1	2	3	4	5
1					
2					
3					
4					

ข้อเสนอแนะ/ปรับปรุง/แก้ไข

1.2 กลิ่นของผลิตภัณฑ์ (ความชอบน้อยไปมาก, 1-5)

สูตรตำรับ	1	2	3	4	5
1					
2					
3					
4					

ข้อเสนอแนะ/ปรับปรุง/แก้ไข

1.3 ลักษณะภายนอกโดยรวม (ความชอบน้อยไปมาก, 1-5)

สูตรตำรับ	1	2	3	4	5
1					
2					
3					
4					

ข้อเสนอแนะ/ปรับปรุง/แก้ไข

2. ลักษณะโดยรวมของผลิตภัณฑ์ (ความชอบน้อยไปมาก, 1-5)

สูตรตำรับ	1	2	3	4	5
1					
2					
3					
4					

ข้อเสนอแนะ/ปรับปรุง/แก้ไข

Figure D-1 The evaluation of satisfaction form

2.   Result of FOS formulation

2.1   The solubility of FOS

The appearance of formulas (color, odor, and turbidity) after kept at room temperature for 1 day and 7 days were observed. The result showed that 60^0 C temperature distilled water made the most soluble and FOS was slightly soluble in 10^0 C temperature distilled water, but some chunk of FOS precipitated at the glass bottom. The characteristics of preparations were shown in Table D-1, D-2 and D-3. The FOS and water ratio of 1:6 was the best to administer because the viscosity was suitable to pour in a spoon.

2.1   The ingredients of the formula

2.2.1   Sweentening agents used in the experiment was glucose and its various concentration (2, 4, 7, 10, and 15%) were tried. All products formulated with different concentrations of glucose did not crack after keeping at room temperature for 7 days with assessment of satisfaction in 10 volunteers (Table D-4). The formula containg 7% glucose formula had the highest score of satisfaction (3.2 ± 1.2). Therefore, the 7% glucose preparation was selected to be added with 1% parabens, flavoring and coloring agents in the next steps.

Table D-1 Physical appearances of FOS solution using 28° C distilled water as a solvent

Proportion of FOS and distilled water (g/ml)	Immediately observed			1-day storage		7-day storage		
	Solubility	Appearance	Viscosity[1]	Appearance	Viscosity[1]	Appearance	Viscosity[1]	Dispersion
1:1	slightly soluble	ND	ND	ND	ND	ND	ND	ND
1:2	partially soluble	ND	ND	ND	ND	ND	ND	ND
1:3	partially soluble	ND	ND	ND	ND	ND	ND	ND
1:4	soluble	clear solution	-	white solution	++	separated suspension	+++	well
1:5	well soluble	clear solution	-	white solution	++	separated suspension	+++	well
1:6	well soluble	clear solution	-	white solution	++	separated suspension	++	well
1:7	well soluble	clear solution	-	white solution	+	separated suspension	+	well
1:8	well soluble	clear solution	-	white solution	+	separated suspension	+	well
1:9	well soluble	clear solution	-	white solution	-	separated suspension	-	well
1:10	well soluble	clear solution	-	white solution	-	separated suspension	-	well

[1] The viscosity level : - = not viscous, + = viscous, if more + = more viscous

ND = not detected

Table D-2 Physical appearances of FOS solution using 60° C distilled water as a solvent

Proportion of FOS and distilled water (g/ml)	Immediately observed			1-day storage		7-day storage		
	Solubility	Appearance	Viscosity[1]	Appearance	Viscosity[1]	Appearance	Viscosity[1]	Dispersion
1:1	partially soluble	ND	ND	ND	ND	ND	ND	ND
1:2	partially soluble	ND	ND	ND	ND	ND	ND	ND
1:3	soluble	clear solution	-	white suspension	+++	white semi-solid	ND	ND
1:4	well soluble	clear solution	-	white solution	+	separated suspension	+++	low
1:5	well soluble	clear solution	-	white solution	+	separated suspension	++	low
1:6	well soluble	clear solution	-	white solution	+	separated suspension	++	low
1:7	well soluble	clear solution	-	white solution	-	separated suspension	+	low
1:8	well soluble	clear solution	-	white solution	-	separated suspension	+	low
1:9	well soluble	clear solution	-	white solution	-	separated suspension	-	low
1:10	well soluble	clear solution	-	white solution	-	separated suspension	-	low

[1] The viscosity level : - = not viscous, + = viscous, if more + = more viscous

ND = not detected

Table D-3 Physical appearances of FOS solution using 10° C distilled water as a solvent

Proportion of FOS and distilled water (g/ml)	Immediately observed			1-day storage			7-day storage	
	Solubility	Appearance	Viscosity[1]	Appearance	Viscosity[1]	Dispersion	Appearance	Viscosity[1]
1:1	not soluble	ND	ND	ND	ND	ND	ND	ND
1:2	slightly soluble	ND	ND	ND	ND	ND	ND	ND
1:3	slightly soluble	ND	ND	ND	ND	ND	ND	ND
1:4	partially soluble	white suspension	-	white semi-solid	ND	ND	ND	ND
1:5	partially soluble	white suspension	-	white semi-solid	ND	ND	ND	ND
1:6	partially soluble	white suspension	-	white semi-solid	ND	ND	ND	ND
1:7	partially soluble	white suspension	-	separated suspension	-	low	ND	ND
1:8	partially soluble	white suspension	-	separated suspension	-	low	ND	ND
1:9	partially soluble	white suspension	-	separated suspension	-	low	ND	ND
1:10	partially soluble	white suspension	-	separated suspension	-	low	ND	ND

[1] The viscosity level: - = not viscous, + = viscous, if more + = more viscous

ND = not detected

Table D-4 The score of satisfaction in various concentrations of glucose in the preparation (n=10 volunteers)

Formula number	% Glucose	Score of satisfaction[1]	
		Mean	SD
1	2	1.00	0.00
2	5	2.20	2.12
3	7	3.20	1.22
4	10	3.00	1.22
5	15	2.70	1.22

[1]score of satisfaction: if 1 = very low, 2 = low, 3 = medium, 4 = good, 5 = very good

2.2.2   Coloring and flavoring agents were added to the preparation to improve the compliance of the patients. Various concentrations of colors and flavors were assessed the satisfaction by 5 volunteers. The selected formulas include as follow (Figure D-2):

1) 0.27% of apple green color and 0.41% of apple flavor.

2) 0.07% of 1% sunset yellow and 0.41% of banana flavor.

3) 0.03% of 5% ponceau 4R and 0.34% of strawberry flavor.

4) 0.14% of 1% orange color and 0.47% of orange flavor.
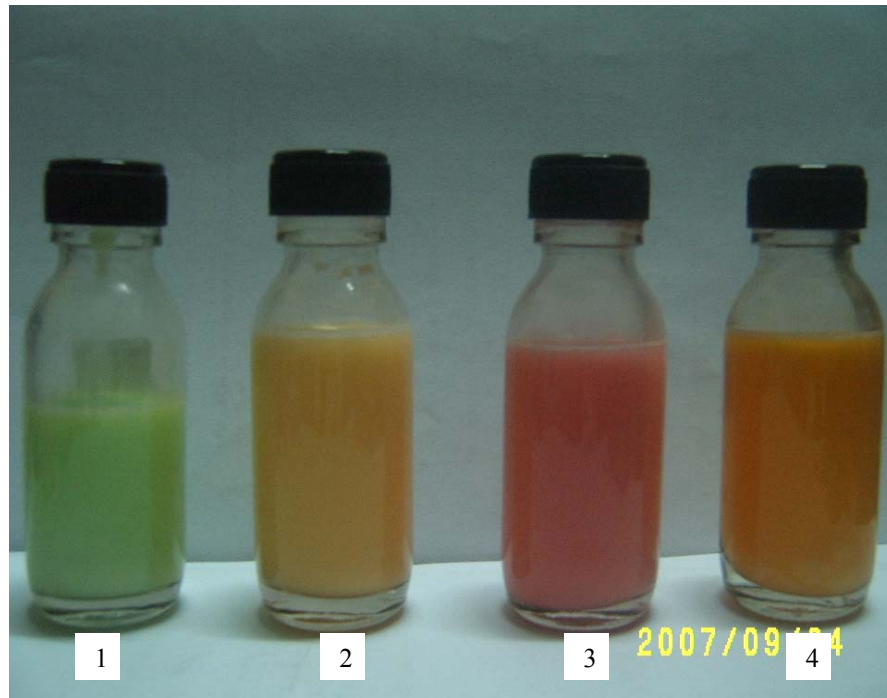
Figure D-2 The characteristic of preparation were added color and flavoring agents:
1 = apple green color, 2 = sunset yellow, 3 = red color, 4 = orange color

2.2   Satisfaction of the preparations

All four preparations were assessed satisfaction in color, odor and appearance by 40 children volunteers at Queen Sirikit National Institute of Child Health. They were evaluated in 5-rating scale from dislike extremely to like extremely. The formula which had the highest score of satisfaction was green-color with apple-flavor formula (Table D-5).

Table D-5 Score of satisfaction in various color, flavor and appearance of the
preparations (n = 40)

Properties	Formula	Mean[1]	SD
Color	Apple green	3.25	1.48
	Sunset yellow	1.85	1.35
	Strawberry	2.45	1.69
	Orange	3.05	1.41
Flavor	Apple	3.28	1.58
	Banana	1.75	1.17
	Strawberry	2.80	1.49
	Orange	3.15	1.48
Appearance	Apple green	3.25	1.71
	Banana	2.00	1.28
	Strawberry	2.70	1.60
	Orange	3.23	1.42
Overall satisfaction	Apple green	3.40	1.63
	Banana	1.98	1.27
	Strawberry	2.33	1.27
	Orange	3.23	1.42

[1] Score of satisfaction :

1 = need improvement, 2 = poor, 3 = fair, 4 = good, 5 = excellent

Table D-6 The physical properties of FOS formulation in appearance and pH after keeping for 0, 14, 30, 60, 90, and 120 days

Characteristics of the Product	Duration of storage (days)					
	0	**14**	**30**	**60**	**90**	**120**
Before reconstitution						
Appearance	green color and clear solution	separate clear green solution in upper and pale green in bottom				
After reconstitution						
Color	green color and clear solution	smooth green color suspension				
Odor	apple flavor	no change				
Viscosity[1]	-	++	++	++	++	++
Taste	sweet	sweet and powder taste				
pH	4.94 ± 0.01	4.96 ± 0.01	5.00 ± 0.01	5.01 ± 0.01	5.03 ± 0.01	5.04 ± 0.01

[1] The viscosity level : - = not viscous, + = viscous, if more + = more viscous

2.3 The stability of the formula

2.4.1 Physical properties of color, odor, taste, and appearance were observed at 0, 14, 30, 60, 90, and 120 days (Table D-6). The formulation did not change in color, odor, taste, turbidity, and packing of suspension when kept for 120 days. In addition, pH of the formula ranged from 4.90-5.10 that was suitable for FOS stability. FOS is not stable in pH below 3 (Bornet, 1994; Franck, 2002).

2.4.2 Microbiological stability was tested by test kit from Department of Health for *Salmonella spp* and *Escherichia coli*. The result showed that the formula was not contaminated with those bacterias after keeping for 30, 60, 90, and 120 days (Table D-7).

Table D-7 The microbiological test for *Salmonella spp* (จ.810) and *Escherichia coli* (จ.111) at 30, 60, 90, and 120 days[1]

Duration of storage (days)	Cool boiled distilled water (negative control)		FOS preparation (sample)		Tap water (positive control)	
	จ.810	จ.111	จ.810	จ.111	จ.810	จ.111
30	-	-	-	-	+	+
60	-	-	-	-	+	+
90	-	-	-	-	+	+
120	-	-	-	-	+	+

[1]Kept in incubator during 24-48 hours and each media did duplicate which interpret bacteria growth in yellow to black (positive in จ.810) and red to yellow (positive in จ.111)
+ positive result
- negative result

3 The appropriated formula used in this study

Rx

-	Fructooligosaccharide (FOS)	10.00	g
-	Glucose	4.20	g
-	Parabens	0.60	ml
-	Apple green color	0.16	ml
-	Apple flavor	0.24	ml
-	Distilled water qs to.	60.00	ml

4 Cost of study laxatives

4.1 The FOS preparation contains FOS 5 g in 30 mL. Net price of FOS preparation was 8.50 baht per dose (per day).

4.2 The MOM suspension contains magnesium hydroxide 2.4 g in 30 mL. Net price of MOM suspension is 4.5 baht per dose (per day).

Appendix E

Statistical analysis

Statistical analysis

The statistics used in this study included

1. Kolmogorov-Smirnov (K-S) test for normal distribution data

2. Independent t-test for comparing mean of two groups before treatment with FOS or MOM (interval scale)

3. Pair-Sample t-test for comparing means before and after treatment in each group

4. Analysis of Variance (ANOVA) for comparing variables three times (0, 2, and 6 weeks) in each group

5 Chi-Square test for comparing frequency of two groups and in each group

The variables of this study included frequency of defecation, stool consistency, total energy, intakes of protein, carbohydrate, lipid, dietary fiber and water, weight, height, BMI, and growth rate.

1. **Normal distribution test**

One-sample Kolmogorov-Smirnov test was used to investigate whether the variables were normally distributed. Data showed that p-value of all tested variables were more than 0.05 (Table E-1). It suggested that parametric statistics could be used to compare mean of variables in this study.

Table E-1 The normal distribution test of variables by Kolmogorov-Smirnov test

Variables	K-S value	*p*-value
Energy intake	1.265	0.173
Protein intake	0.675	0.750
Fat intake	0.480	0.946
Carbohydrate intake	0.838	0.508
Fiber intake	1.278	0.142
Water intake	0.945	0.399
Weight	1.186	0.197
Height	1.349	0.140
BMI	1.231	0.090
Stool frequency	1.156	0.200
Stool consistency	1.194	0.224

2. The comparison of means between the MOM and FOS groups by using Independent t-test.

Before treatment

By Independent t-test, the data showed that *p*-value was more than 0.05 in all comparisons (Table E-2). It indicated that all means of variables in the MOM and FOS groups were not significantly different at baseline.

After 2 weeks

By Independent t-test, the data showed that *p*-value was more than 0.05 in all comparisons (Table E-3). It indicated that all means of variables in the MOM and FOS groups were not significantly different after 2-week treatment.

After 6 weeks

By Independent t-test, the data showed that *p*-value was more than 0.05 in all

comparisons (Table E-4). It indicated that all means of variables in the MOM and FOS groups were not significantly different at the end of the study.

Table E-2 The comparison of mean variables in the MOM and FOS groups at baseline

Variables	groups	n	mean	SD	t	*p*-value
Weight (kg)	FOS	25	25.54	10.10	2.86	0.097
	MOM	29	21.89	8.43		
Height (cm)	FOS	25	121.28	18.59	3.58	0.064
	MOM	29	115.86	13.08		
BMI (kg/m^2)	FOS	25	16.56	2.40	1.00	0.321
	MOM	29	15.89	3.48		
Total energy (kcal)	FOS	25	1042.80	247.09	0.01	0.932
	MOM	29	1075.40	243.81		
Protein (kcal)	FOS	25	291.56	61.44	2.13	0.167
	MOM	29	296.44	109.20		
Fat (kacl)	FOS	25	409.95	214.29	3.19	0.096
	MOM	29	398.43	119.61		
Carbohydrate (kcal)	FOS	25	422.24	135.56	1.26	0.28
	MOM	29	456.44	181.88		
Fiber (g)	FOS	25	8.01	3.28	0.05	0.835
	MOM	29	7.51	3.77		
Water (g)	FOS	25	939.50	287.36	0.93	0.352
	MOM	29	863.37	216.52		
Frequency of defecation (times/week)	FOS	25	1.36	0.49	1.62	0.208
	MOM	29	1.28	0.45		
Stool consistency	FOS	25	1.80	0.58	3.34	0.073
	MOM	29	1.55	0.69		

Table E-3 The comparison of mean variables in the MOM and FOS groups at 2-week

treatment

Variables	groups	n	mean	SD	t	p-value
Weight (kg)	FOS	25	25.90	10.20	3.39	0.071
	MOM	29	22.36	8.33		
Height (cm)	FOS	25	121.90	18.64	3.61	0.063
	MOM	29	116.36	13.04		
BMI (kg/m^2)	FOS	25	16.77	2.35	0.58	0.451
	MOM	29	16.11	3.34		
Frequency of defecation (times/week)	FOS	25	4.03	1.34	0.01	0.915
	MOM	29	4.34	1.25		
Stool consistency	FOS	25	4.39	0.64	2.17	0.146
	MOM	29	4.64	0.82		

Table E-4 The comparison of mean variables in the MOM and FOS groups at the end

      of the study

Variables	groups	n	mean	SD	t	p-value
Weight (kg)	FOS	25	26.22	10.33	3.68	0.061
	MOM	29	22.47	8.30		
Height (cm)	FOS	25	122.30	18.56	3.57	0.064
	MOM	29	116.47	12.97		
BMI (kg/m^2)	FOS	25	16.86	2.36	0.66	0.419
	MOM	29	16.18	3.33		
Total energy (kcal)	FOS	25	1507.80	559.41	0.14	0.715
	MOM	29	1599.90	532.52		
Protein (kcal)	FOS	25	325.52	86.84	2.95	0.046
	MOM	29	414.04	156.88		
Fat (kcal)	FOS	25	482.76	269.82	1.33	0.039
	MOM	29	631.44	225.72		
Carbohydrate (kcal)	FOS	25	688.20	272.52	0.45	0.514
	MOM	29	545.68	216.72		
Fiber (g)	FOS	25	18.43	4.97	0.29	0.601
	MOM	29	14.46	4.98		
Water (g)	FOS	25	1444.10	451.83	0.96	0.344
	MOM	29	1287.20	347.08		
Frequency of defecation (times/week)	FOS	25	5.14	1.24	0.94	0.338
	MOM	29	5.87	1.11		
Stool consistency	FOS	25	4.45	0.50	2.69	0.107
	MOM	29	4.58	0.68		

3. **The comparison of means between before and after treatments by using Pair-Sample t-test.**

By Pair-Sample t-test, the data showed that *p*-value was less than 0.05 in all comparisons except protein and fat intake in the FOS group (Table E-5 and E-6). It indicated that all means of variables in the MOM group significantly increased after treatment. In the FOS group, the means of energy, carbohydrate, fiber and water intakes significantly increased after treatment but protein and fat intakes did not significantly change.

Table E-5 The comparison of mean variables in the FOS group at 0, 6 weeks

Variables	week	n	mean	SD	t	*p*-value
Frequency of defecation (times/week)	0	25	1.36	0.49	15.56	<0.001
	6	25	5.14	1.24		
Stool consistency	0	25	1.80	0.58	22.32	<0.001
	6	25	4.45	0.50		
Total energy (kcal)	0	25	1042.80	247.09	2.38	0.049
	6	25	1507.80	559.41		
Protein (kcal)	0	25	291.56	61.44	0.73	0.488
	6	25	325.52	86.84		
Fat (kacl)	0	25	409.95	214.29	0.75	0.475
	6	25	482.76	269.82		
Carbohydrate (kcal)	0	25	422.24	135.56	3.12	0.017
	6	25	688.20	272.52		
Fiber (g)	0	25	8.01	3.28	4.40	0.003
	6	25	18.43	4.97		
Water (g)	0	25	939.50	287.36	2.37	0.049
	6	25	1444.10	451.83		

Table E-6 The comparison of mean variables in the MOM group at 0, 6 weeks

Variables	week	n	mean	SD	t	p-value
Frequency of defecation (times/week)	0	29	1.28	0.45	22.438	<0.001
	6	29	5.87	1.11		
Stool consistency	0	25	1.55	0.69	17.45	<0.001
	6	25	4.58	0.68		
Total energy (kcal)	0	25	1075.40	243.81	3.09	0.017
	6	25	1599.90	532.52		
Protein (kcal)	0	25	296.44	109.20	3.39	0.012
	6	25	414.04	156.88		
Fat (kacl)	0	25	398.43	119.61	2.57	0.037
	6	25	631.44	225.72		
Carbohydrate (kcal)	0	25	456.44	181.88	2.78	0.027
	6	25	545.68	216.72		
Fiber (g)	0	25	7.51	3.77	3.27	0.014
	6	25	14.46	4.98		
Water (g)	0	25	863.37	216.52	2.52	0.04
	6	25	1287.20	347.08		

4. The comparison of means among three times period of treatment by using Analysis of Variance.

By ANOVA test, data showed that p-value of variables frequency of defecation and stool consistency were less than 0.05 in both FOS and MOM groups, whereas those of variables weight, height and BMI were more than 0.05 (Table E-7 and E-8). It indicated that defecation pattern in both groups changed significantly after treatment but weight, height and BMI did not significantly change, however, they tended to increase.

Table E-7 The comparison of mean variables in the FOS group in each period

Variables	week	n	mean	SD	F	p-value
Frequency of defecation (times/week)	0	25	1.36	0.49	79.07	<0.001
	2		4.03	1.34		
	6		5.14	1.24		
Stool consistency score	0	25	1.80	0.58	172.58	<0.001
	2		4.39	0.64		
	6		4.45	0.50		
Weight (kg)	0	25	25.54	10.10	0.03	0.973
	2		25.90	10.20		
	6		26.22	10.33		
Height (cm)	0	25	121.28	18.59	0.01	0.995
	2		121.90	18.64		
	6		122.30	18.56		
BMI (kg/m^2)	0	25	16.56	2.40	0.10	0.901
	2		16.77	2.35		
	6		16.86	2.36		

Table E-8 The comparison of mean variables in the MOM group in each period

Variables	week	n	mean	SD	F	p-value
Frequency of defecation (times/week)	0	29	1.28	0.45	158.24	<0.001
	2		4.34	1.26		
	6		5.87	1.11		
Stool consistency score	0	29	1.55	0.69	168.59	<0.001
	2		4.64	0.82		
	6		4.58	0.68		
Weight (kg)	0	29	21.89	8.43	0.04	0.962
	2		22.36	8.33		
	6		22.47	8.30		
Height (cm)	0	29	115.86	13.08	0.02	0.982
	2		116.36	13.04		
	6		116.47	12.97		
BMI (kg/m^2)	0	29	15.89	3.48	0.06	0.944
	2		16.11	3.34		
	6		16.18	3.33		

5. **The comparison of frequency in the MOM and FOS groups also with in each group by using Chi- Square test.**

Comparing between the MOM and FOS groups at baseline and the end of the study.

By Chi-Square test, the data showed that p-value was more than 0.05 in all comparisons (Table E-9 and E-10). It indicated that all means of variables in the MOM and FOS groups were not significantly different at baseline and at the end of treatment.

Comparing between baseline and the end of the study in each groups.

By Chi-Square test, the data showed that p-value was less than 0.05 in all comparisons except frequency of urge, incontinent during defecation and time spent in each defecation in the FOS group (Table E-11 and E-12). It indicated that all comparisons except frequency of urge and flatulence during defecation in the MOM group significantly better after treatment.

Table E-9 The comparison of frequency variables in the MOM and FOS groups at

baseline.

Variables	χ^2	df	p-value
Sex	0.021	1	0.884
Age	5.646	8	0.687
Nutrition status	0.215	1	0.643
Degree of education	4.089	3	0.252
Illness	0.563	2	0.755
Frequency of vegetable intake	2.518	1	0.113
Proportion of fiber intake per day	2.518	1	0.113
Amount of water intake per day	2.518	1	0.113
Carbonated beverage intake	0.001	1	0.991
Soft drink intake	0.001	1	0.973
Fruit juice intake	2.399	1	0.121
Snack intake	1.432	1	0.121
How to go to school	1.768	3	0.622
Time spent in watching television per day	5.085	4	0.279
Time spent in playing computer per day	1.043	2	0.592
Time spent in reading cartoon book per day	2.607	2	0.272
Time spent in running outside per day	0.952	2	0.621
Number of days of exercise per week	2.875	3	0.411
Duration of exercise per each	2.115	4	0.715
Frequency of defecation	NA		
Characteristic of feces	1.182	1	0.277
Frequency of straining during defecation	3.143	4	0.534
Frequency of pain at anus during defecation	1.610	4	0.807
Frequency of feeling incomplete evacuation	8.873	4	0.064

Table E-9 The comparison of frequency variables in the MOM and FOS groups at

baseline (continued).

Variables	χ^2	df	p-value
Frequency of urge during defecation	1.344	4	0.854
Time spent in each defecation	4.626	4	0.328
Having stomachache during defecation	0.851	1	0.356
Having flatulence during defecation	0.088	1	0.767
Having incontinent during defecation	0.038	1	0.845
Feeling pain at anus during defecation	NA		
Having blood in feces	2.136	1	0.144
Frequency of withhold feces	4.212	4	0.378

Table E-10 The comparison of frequency variables in the MOM and FOS groups at

the end of the study.

Variables	χ^2	df	p-value
Frequency of defecation	3.270	3	0.361
Characteristic of feces	0.600	1	0.440
Frequency of straining during defecation	NA		
Frequency of pain at anus during defecation	NA		
Frequency of feeling incomplete evacuation	NA		
Frequency of urge during defecation	NA		
Time spent in each defecation	0.400	1	0.531
Having stomachache during defecation	0.024	1	0.877
Having flatulence during defecation	2.410	1	0.121
Having incontinent during defecation	NA		
Feeling pain at anus during defecation	NA		
Having blood in feces	NA		
Frequency of withhold feces	0.550	2	0.761

Table E-11 The comparison of frequency variables in the FOS group at 0, 6 weeks

Variables	χ^2	df	p-value
Frequency of straining during defecation	46.150	4	<0.001
Frequency of pain at anus during defecation	46.150	4	<0.001
Frequency of feeling incomplete evacuation	36.210	4	<0.001
Frequency of urge during defecation	6.820	4	0.146
Time spent in each defecation	6.830	4	0.145
Having stomachache during defecation	26.300	1	<0.001
Having flatulence during defecation	NA		
Having incontinent during defecation	3.190	1	0.074
Feeling pain at anus during defecation	50	1	<0.001
Having blood in feces	9.520	1	0.002
Frequency of withhold feces	25.670	4	<0.001

Table E-12 The comparison of frequency variables in the MOM group at 0, 6 weeks

Variables	χ^2	df	p-value
Frequency of straining during defecation	54.130	3	<0.001
Frequency of pain at anus during defecation	50.520	4	<0.001
Frequency of feeling incomplete evacuation	22.100	3	<0.001
Frequency of urge during defecation	9.280	4	0.054
Time spent in each defecation	12.060	3	0.007
Having stomachache during defecation	23.73	1	<0.001
Having flatulence during defecation	3.160	1	0.075
Having incontinent during defecation	4.300	1	0.038
Feeling pain at anus during defecation	58	1	<0.001
Having blood in feces	20.230	1	<0.001
Frequency of withhold feces	37.330	4	<0.001

Appendix F

Product data sheet of FOS

Product Data Sheet

Frutafit® HD

Description

Frutafit®HD is a native inulin / fructo-oligosaccharide (FOS). It is a *natural* powdered food ingredient based on chicory inulin with a high purity. Due to its physiological and technological characteristics, Frutafit®HD can be applied in a wide range of food products.

Inulin from chicory is a polydisperse mixture of linear fructose polymers with mostly a terminal glucose unit, coupled by means of $\beta(2-1)$ bonds.

Specification

Physical aspects
Dry matter content   95-99%

Composition on dry matter
Inulin (DP2-DP60)   90-95%
Fibre (AOAC 997.08)   90-95%
Fructose, glucose, sucrose   5-10%
Average chain length   8-12 monomers
Ash $\leq 0.2\%$
Heavy metals   complies with legal requirements

Microbiology
Aerobic plate count $\leq$ 2000 CFU/gram
Thermophilic plate count $\leq$ 2000 CFU/gram
Moulds $\leq$ 20 CFU/gram
Yeasts $\leq$ 20 CFU/gram
Bacillus cereus $\leq$100 CFU/gram
Enterobacteriaceae   absent in 1 gram
Staphylococcus aureus   absent in 1 gram
Salmonella   absent in 25 grams

Nutritional information

Average values per 100 grams Frutafit®HD:
- Carbohydrates:
   - digestible (fructose, glucose, sucrose)   7 grams
   - non-digestible (dietary fibre, inulin)   90 grams
- Proteins   0 gram
- Fats   0 gram
- Cholesterol   absent
- Dietary fibres (AOAC 997.08)   90 grams
- Sodium   40 mg
- Calcium   11.5 mg
- Potassium   7.5 mg
- Iron   0.4 mg
- Other minerals   negligible
- Vitamins   negligible
- Gluten   absent
- Lactose   absent
- Folate   absent
- Insecticides, pesticides   absent
- Enzymatic activity   absent
- Colour, flavour, preservatives   absent

Calorific value   1,6 kcal/gram[1]
Glycaemic Index (GI) value   1[2]

[1] calculated value based on 1.5 kcal/gram pure inulin that has been established in scientific studies. Please check local legislation and adapt if necessary.
[2] The effect on the blood glucose level of 25 gram carbohydrate coming from Frutafit® HD is compared with the effect on blood glucose level of 25 gram glucose (control=100).

Additional product characteristics

- Appearance   fine white powder
- Dispersability   good
- Wettability   good
- pH   neutral
- Taste   neutral, slightly sweet
- Tapped density   550 ± 100 gram/litre

These data are indicative and only meant to provide additional information.

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Other information

Packaging
20 kg, white multi layer paper bag with coloured PE inner liner

Labelling
In the ingredient list inulin/fructo-oligosaccharide can be declared as an ingredient, not an additive. The product can be labelled as inulin, fructo-oligosaccharide or polyfructose. In the US, Frutafit® inulin is officially recognised as GRAS.

Safety
GRAS status. FDA approved, notice no. GRN 000118

Storage
The product should be stored under dry conditions in the original unopened bag.

Shelf life
When stored in unopened bags under dry conditions, the product can be stored for at least 5 years after production date. Best before date is printed on each individual bag.

GMO
For the production of this product, Sensus only uses raw materials from conventionally cultivated chicory varieties. Therefore no labelling as a GMO derived ingredient is needed for application of this product according to the regulations EC (2001/18), EC (1829/2003), EC(1830/2003).

Allergens
Neither the raw material nor the process additives used in the production of this product contain the following allergens: gluten, components from milk, soy, nuts, fruit, eggs, meat or fish.

Kosher
Certified by circle K.

Halal
Certified by Halal Correct

Analyses
Fructans (inulin/fructo-oligosaccharides) in food products can be analysed by the following methods: AOAC 997.08 (AACC 32-31) and AOAC 999.03 (AACC 32-32).

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December 2004

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