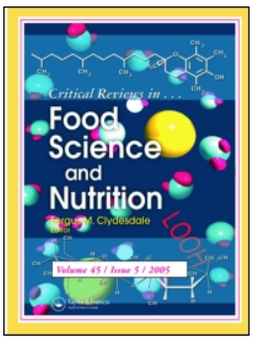

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Putative mechanisms of kiwifruit on maintenance of normal gastrointestinal function

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ABSTRACT

Kiwifruits are recognized as providing relief from constipation and symptoms of constipation-predominant irritable bowel syndrome (IBS-C). However, the underlying mechanisms, specifically in regards to gastrointestinal transit time and motility, are still not completely understood. This review provides an overview on the physiological and pathophysiological processes underlying constipation and IBS-C, the composition of kiwifruit, and recent advances in the research of kiwifruit and abdominal comfort. In addition, gaps in the research are highlighted and scientific studies of other foods with known effects on the gastrointestinal tract are consulted to find likely mechanisms of action. While the effects of kiwifruit fiber are well documented, observed increases in gastrointestinal motility caused by kiwifruit are not fully characterized.

There are a number of identified mechanisms that may be activated by kiwifruit compounds, such as the induction of motility via protease-activated signaling, modulation of microflora, changes in colonic methane status, bile flux, or mediation of inflammatory processes.

Abbreviations: IBS: irritable bowel syndrome; IBS-C: constipation predominant irritable bowel syndrome; SCFA: short chain fatty acid; ENS: enteric nervous system; MMC: migrating motor complex; CCK: cholecystokinin; EC: enterochromaffin; IL: interleukin; SERT: serotonin selective re-uptake transporter; SCT: slow colonic transit; ICC: Interstitial Cells of Cajal; TLR: toll-like receptor; TNFα: tumor necrosis factor alpha; FODMAP: fermentable oligosaccharides, disaccharides, monosaccharides and polyols; CPI: cysteine-proteinase inhibitor; GABA: gamma-aminobutyric acid; COX2: cyclooxygenase 2; NO: nitric oxide; PAR: protease activated receptor; PGE: prostaglandin; LPS: lipopolysaccharide

KEYWORDS
Kiwifruit; kissper; motility; actinidin; constipation; IBS

1. Introduction

Constipation and irritable bowel syndrome (IBS) are both chronic functional gastrointestinal disorders (Mearin et al., 2016). About 11.2% of adults suffer from IBS worldwide, with a higher prevalence for women (Lovell and Ford, 2012), and constipation may be present in up to 29% of the population, depending on the definition used (Bharucha et al., 2013; Choung et al., 2007; Garrigues et al., 2004; Pare et al., 2001). Both constipation and IBS have a severe negative impact on quality of life (Badia et al., 2002; Bharucha et al., 2013; Chang, 2004; Halder et al., 2004; Koloski et al., 2000). Since both disorders are common and chronic, the demand to manage abdominal discomfort and constipation by safer, cost effective and natural remedies is high. There is evidence that the kiwifruit, *Actinidia deliciosa*, cultivar 'Hayward' (referred to as green kiwifruit throughout this review) fulfills these requirements. Green kiwifruit has been used and promoted to maintain abdominal comfort for many years (Ferguson and Ferguson, 2003), and has been studied more recently under controlled settings (Chan et al., 2007; Chang et al., 2010; Rush et al., 2002). In these studies, the consumption of green kiwifruit significantly decreased abdominal discomfort in individuals with either constipation predominant IBS (IBS-C) or in healthy elderly individuals suffering from constipation, without reported side effects. There are a number of theories concerning the potential mechanisms of action for green kiwifruit to produce these clinical effects, for example the presence of the protease actinidin (Pastorello et al., 1998) and specific characteristics of kiwifruit fiber (Chang et al., 2010). However, the mechanism underlying the observed effects of green kiwifruit consumption on constipation and IBS-C are yet to be fully elucidated. What is especially interesting is the consumption of kiwifruit does not negatively affect healthy individuals with regard to bowel habit. This review aims to identify known and putative mechanisms of action for compounds present in green kiwifruit.

The present article discusses the physiological function of the digestive system, the pathophysiological mechanisms

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behind functional constipation and IBS-C, the composition of green kiwifruit, foods and compounds similar to green kiwifruit with known effects on the gastrointestinal tract, a summary of the work covering the effects of green kiwifruit on the gut, as well as hypothetical mechanisms behind the gastrointestinal effects of green kiwifruit.

2. Physiology of the digestive system

The function of the digestive system is the breakdown of complex food molecules for absorption of nutrients, water and minerals and to expel indigestible matter. To fulfill these functions, the digestive system is highly specialized. The stomach secretes hydrochloric acid and pepsin, an enzyme that breaks down protein into peptides and amino acids. The small intestine is responsible for digestion and absorption. Bicarbonate, bile and pancreatic enzymes are secreted into the proximal small intestine, while enzymes to digest di-saccharides are brush-border bound (Brownlee, 2011). The uptake of nutrients involves carrier proteins as well as passive diffusion, and water as well as water soluble nutrients follow electrolytes via osmosis (Biesalski, 2004; Brownlee, 2011).

The colon is responsible for the resorption of water (Andrews and Storr, 2011). Sodium is actively transported out of the lumen and epithelial cells, and water follows passively (Biesalski, 2004). The colon hosts the microflora, a very large, diverse and personally-specific microbial population. The flora consists mainly of *Bacteroides* and *Clostridium* species, and less than 2% belong to *Lactobacillus* and *Bifidobacteria species* (Sghir et al., 2000). These bacteria interact with their host via metabolites (Macfarlane and Macfarlane, 1997) and surface patterns which are recognized by immune cells (Abreu et al., 2005). The microflora feeds on undigested nutrients in the colonic lumen, and produces metabolites such as short chain fatty acids (SCFA) (Cook and Sellin, 1998), Vitamin K (which can be taken up by the host), and gases such as hydrogen and methane (Biesalski, 2004).

The enteric nervous system (ENS) is the major driver of gastrointestinal motility (Gershon, 2008), and is responsible for the mechanical propulsion of digesta through the gastrointestinal tract. Motility, comprising both the low amplitude motor complex (responsible for mixing) and the high-amplitude migrating motor complex (MMC, propulsive in nature), is regulated through the release of neurotransmitters. Neurotransmitters, such as cholecystokinin (CCK), signal satiation, while gastrin increases secretion and gastric peristalsis. CCK, which is secreted in response to the presence of nutrients in the lumen of the small intestine, also reduces gastric emptying and pancreatic secretion. Pressure-sensitive enterochromaffin cells (EC-cells) secrete serotonin (Bulbring and Crema, 1959a, b; Chen et al., 1998; Wade et al., 1996), which is a major regulator of gastrointestinal motility, pancreatic secretion, and visceral sensation (Camilleri, 2002; Gershon, 1999; Grider et al., 1998). All four mediators also increase the motility of the small intestine, with propulsion predominantly being induced by serotonin (Andrews and Storr, 2011). Another neurotransmitter, peptide YY, effectively reduces motility and secretion. Peptide YY also regulates the absorption of electrolytes and water in the colon (El-Salhy et al., 2002; Okuno et al. 1992; Spiller et al., 1988).

3. Characterization of constipation and IBS

The Rome IV criteria defines chronic functional constipation as the presence of at least two of the following: hard and lumpy feces, feelings of incomplete evacuation and anorectal blockage, less than three bowel movements per week, straining, and the need for digital maneuvers to facilitate evacuation for more than 25% of the time, absence of loose feces without laxatives, and no IBS (Mearin et al., 2016). These symptoms should occur for more than six months, with symptoms present during the last three months before presentation of the patient.

IBS is a chronic functional disorder. Individuals suffering from IBS experience recurrent abdominal pain at least once per week related to defecation, associated with a change in fecal frequency and fecal form. As described in the Rome IV criteria (Mearin et al., 2016) IBS is classified into subtypes based on the predominant fecal form (>25%) according to the Bristol stool chart (Mearin et al., 2016; Tillisch et al., 2005). Functional gastrointestinal disorders such as IBS-C and constipation are complex and involve a variety of pathophysiological mechanisms (Barbara et al., 2016; Boeckxstaens et al., 2016; Mearin et al., 2016; Vanner et al., 2016). Often there will be no obvious trigger for the onset of symptoms, but this may include food intolerances, life style changes, stress, and infective or drug-induced gastroenteritis. For IBS-C, the putative pathophysiological mechanisms include visceral afferent hypersensitivity, altered communication between the brain and the ENS, impaired motility, increased permeability of the gut barrier, activation of the immune system and altered microbiota (Mearin et al., 2016). Since constipation and IBS-C are believed to be on the same spectrum, many of these mechanisms are also involved in constipation. However, because of the complex interplay of immune system, microflora and ENS, the pathophysiological mechanisms are interwoven and affect each other.

4. Pathophysiological mechanisms of functional constipation and IBS-C

4.1. Lack of fiber

The first line treatment of functional constipation is to increase the consumption of dietary fiber (Andrews and Storr, 2011; Bharucha et al., 2013; Costilla and Foxx-Orenstein, 2014; Tack and Muller-Lissner, 2009). Dietary fiber is the content of plant-derived food not digested by human enzymes and not absorbed in the small intestine. There are two types of fiber, classified according to their solubility in water: soluble and insoluble fiber. Both types add bulk, increase water retention in the colon (Brownlee, 2011; Chaplin, 2003), and change fecal consistency (McIntyre et al., 1997; Muller-Lissner et al., 2005). Fiber also decreases transit time (McIntyre et al., 1997; Muller-Lissner, 1988). Insoluble fiber delays gastric emptying (Sanaka et al., 2007), while both types of fiber accelerate small intestine transit (Bach Knudsen and Hessov, 1995; Hebden et al., 2002) and colonic transit in some adults (McIntyre et al., 1997).

Fiber is the main food source for the microflora in the gastrointestinal tract. The presence of fiber as an energy source promotes bacterial growth, mostly that of *Lactobacillus* and *Bifidobacteria* species (Brownlee, 2011), which produce SCFA (Cook and Sellin, 1998) and lignans (Rowland et al., 2003).

Both lignans and SCFA are beneficial for the colon, with SCFA being the main energy source for colonocytes (Topping and Clifton, 2001). In addition, SCFA lower the luminal pH, limiting the toxicity of potentially damaging amines, stimulating microfloral growth, and preventing the degradation of primary bile acids (Topping and Clifton, 2001). Without the dietary intake of fiber, the microflora of the colon may use the intestinal mucus layer as a nutritional source (Pickard et al., 2014), and potentially damage the protective mucosa (Brownlee, 2011). In addition, fiber has an abrasive effect on the mucus layer of the intestinal barrier, which is necessary for the maintenance of the barrier (Montagne et al., 2003).

However, lack of fiber may only be a contributing factor in a subgroup of people with constipation (Voderholzer et al., 1997). In some patients with severe constipation, a higher fiber intake may worsen symptoms (Francis and Whorwell, 1994; Muller-Lissner et al., 2005). Soluble fiber appears to be better tolerated by patients and diminishes bloating (Foxx-Orenstein et al., 2008). For those with predominant bloating, the reduction of fiber intake may be beneficial (Quartero et al., 2005; Rao et al., 2015). Increased water intake seems to have no effect on chronic constipation, with or without fiber (Chung et al., 1999; Young et al., 1998; Ziegenhagen et al., 1991).

4.2. Visceral hypersensitivity and serotonin signaling

The sensitivity to pain associated with IBS-C is the biggest difference with functional constipation. Pain is experienced through activation of sensory neurons. Sensory neurons express many receptors, and are activated by a variety of neurotransmitters and other mediators. These mediators are released during inflammation and injury, which can lead to hypersensitivity (Vergnolle, 2008). The source of these neurotransmitters and mediators can be mast cells (Barbara et al., 2007), lymphocytes (Ford and Talley, 2011; Walker et al., 2009), macrophages (Mowat and Bain, 2011; Spiller et al., 2000) and other cell types (Vanner et al., 2016). The expressed mediators include histamines, TNFα, interleukin (IL) 6, serotonin and many more (Barbara et al., 2007; Buhner et al., 2009; Coelho et al., 1998; Cremon et al., 2011; Gershon, 1999). These pro-inflammatory mediators can act directly (Barbara et al., 2007) or indirectly (Dietrich et al., 2010) on nerves, and can trigger peristaltic reflexes or desensitize neurons (Chen et al., 2001; Chen et al., 1998; Vanner et al., 2016). Prolonged sensitization of neurons may even change neuronal gene expression (Vergnolle, 2008) and lead to alterations within the central nervous system (Woolf, 2011).

Another mechanism underlying constipation and IBS-C may be impaired signaling by serotonin (Figure 1). To negate a signal caused by serotonin, serotonin is taken up by enterocytes via serotonin selective re-uptake transporters (SERT) (Chen et al., 1998; Wade et al., 1996). The expression of SERT has been shown to be reduced in IBS-C (Mawe et al., 2006). In addition, the inhibition of serotonin re-uptake by selective serotonin re-uptake inhibitors for depression shows effects similar to those in IBS (Chen et al., 1998). Studies on serotonin plasma concentrations in patients with IBS-C are conflicting (Dunlop et al., 2005; Keszthelyi et al., 2013; Manocha and Khan, 2012), however mucosal serotonin concentrations appear to be low (Keszthelyi et al., 2013). Long-term exposure of receptors to

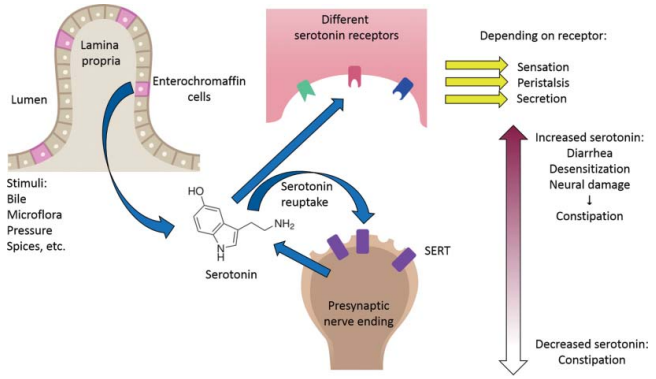

Figure 1. Serotonin signaling and the effects. SERT= Serotonin selective reuptake transporter. Adapted from (Barbara et al., 2016) with permission.

serotonin might also cause a compensational effect, which may explain the confusing findings of both increased and decreased mucosal serotonin availability (Coates et al., 2004; Gershon and Tack, 2007; Miwa et al., 2001). Serotonin receptors may be expressed differently in people with constipation (Zhao et al., 2003), which may favor inhibition of motility. A difference in serotonin signaling may also explain the high prevalence of IBS-C in women (Meleine and Matricon, 2014): progesterone decreases SERT levels (Pecins-Thompson et al., 1998), and in slow transit constipation, progesterone receptors are increased in epithelial cells (Guarino et al., 2011) and in smooth muscle cells (Cheng et al., 2008). An increase of serotonin availability by pharmacological agonists and antagonists improved abdominal comfort and increased bowel movements in adults with constipation (Bouras et al., 2001; Emmanuel et al., 2002) and IBS-C (Camilleri et al., 1999; Hoffman et al., 2012), albeit modestly (Ford et al., 2009).

4.3. Impaired gastrointestinal motility

Abnormally slow colonic transit time has been observed in subsets of patients with IBS-C and constipation (Bouchoucha et al., 2006; Camilleri et al., 2008; Manabe et al., 2010; Rao et al., 2009; Tornblom et al., 2012). In recent years, more studies have implicated neuronal problems within the ENS in the onset of constipation and slow colonic transit (SCT) in some patients (Bassotti and Villanacci, 2006; Knowles et al., 2001). Contractility may be altered, with less propulsive migrations observed in the colon (Grotz et al., 1993; Schiller, 2004). Especially in patients with SCT, the electric neuronal signals inducing contractions have been found to be weak or even absent (Shafik et al., 2003). The Interstitial Cells of Cajal (ICC) act as gastrointestinal pacemakers and are responsible for these electronic signals (Torihashi et al., 1995). If the ICC are inactive in an intestinal segment, the motility of the colon might diminish (Ward et al., 1995; Ward et al., 1994). With decreased propulsive colonic contractions, fecal matter may not be transported effectively (Bassotti et al., 2003). In patients with constipation and SCT, ICC numbers were found to be lower than in healthy controls, even completely absent in the submucosal border (Tong et al., 2004). In addition, glial cells and enteric ganglial cells were reduced, and the enteric neurons of patients showed significant signs of apoptosis. However, if this is cause or consequence of slow colonic transit is, as yet, unclear.

A body of evidence suggests an association between methane and intestinal transit, however the causal relationship remains unclear (Jahng et al., 2012; Sahakian et al., 2010). Possible mechanisms include: methanogens favor proliferation in an environment of slower transit, or methanogens may compete for a common substrate such as hydrogen, or methane itself may be a bioactive molecule that directly affects intestinal transit and is involved in the regulation of intestinal motor function, or methane potentially influences the neurotransmitter serotonin which is involved in peristaltic control of the gut (Sahakian et al., 2010).

4.4. Altered intestinal permeability and secretion

The intestinal epithelial barrier is one of the most important features of the gastrointestinal system, since it separates the immune system from the intestinal lumen and the microflora, and is also responsible for water retention in the colon (Figure 2). The barrier consists of a layer of mucus made from mucins and antimicrobial peptides secreted by epithelial goblet cells (Kim and Ho, 2010), the microflora on and in the top layer of the mucus, the epithelium itself, and the immune cells underneath the epithelium (Johansson et al., 2013). Impairment of the barrier can lead to inflammation and allergies. Evidence is growing that intestinal permeability is altered in IBS and other functional gastrointestinal disorders. The exact cause for altered intestinal permeability is unclear, but genetic factors, such as a polymorphisms in genes encoding proteins necessary for the tight junctions in the epithelium (Vanner et al., 2016), decreased concentrations of enzymes important for barrier maintenance (Zhou et al., 2010), stress-related activation of mast cells (Guilarte et al., 2007), and a change in proteolytic activity within the gut lumen (Gecse et al., 2008) are able to contribute to altered intestinal permeability. Since colonic permeability is high in all IBS subtypes (Vivinus-Nebot et al., 2012), increased permeability to luminal antigens could contribute to constipation and IBS-C. Effective pharmacological treatment for IBS-C and constipation includes agents which increase gastrointestinal secretion (Chey et al., 2012; Rao et al., 2012). However, studies demonstrating altered secretion in IBS-C and constipation are limited. Serotonin, which has been found to be altered in chronic constipation (El-Salhy et al., 1999) and IBS-C (Coates et al., 2004; Gershon, 2003; Gershon and Tack, 2007; Miwa et al., 2001), is also known to modulate secretion of pancreatic fluids via serotonin receptors (Gershon, 1999). Another neuropeptide that is involved in intestinal secretion is peptide YY. Peptide YY controls the absorption of electrolytes and water in the colon (El-Salhy et al., 2002; Okuno et al. 1992; Spiller et al., 1988). While studies reporting changes in the presence of peptide YY secreting cells and peptide YY concentrations in tissue extracts in constipation have been so far inconclusive (el-Salhy and Norrgard, 1998; El-Salhy et al., 1999; Sjolund et al., 1997), an increase of peptide YY would be expected to decrease the secretion of water and electrolytes into the colon, as well as increase resorption of water (El-Salhy et al., 2002).

Other neuropeptides that have abnormal patterns in constipation are enteroglucagon and somatostatin, which decrease motility (El-Salhy et al., 1999), and vasoactive intestinal peptide, which induces secretion of water and motility (Sjolund et al., 1997). Bile acids are also involved in both secretion and motility (Shin et al., 2013). Bile acids increase serotonin availability by stimulation of EC-cells (Kidd et al., 2008; Peregrin et al., 1999), and alter the intestinal microflora (Floch, 2002; Islam et al., 2011). Oral supplementation of bile acids increases transit in IBS-C (Rao et al., 2010). Changes in bile salt metabolism may be involved in the pathogenesis of constipation (Abrahamsson et al., 2008; Rao et al., 2010).

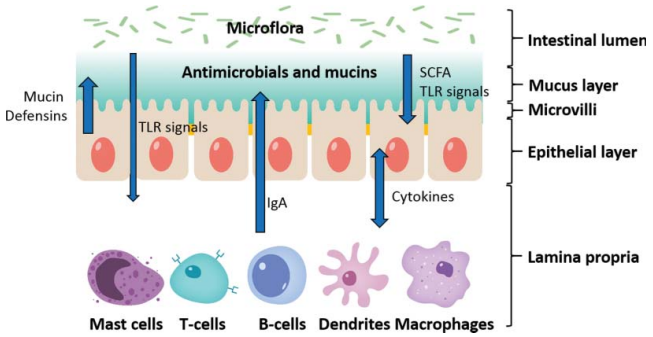

Figure 2. Intestinal permeability and barrier structure. The microflora can effect epithelial cells, mucin turnover, and immune system function, while the immune cells also effect the epithelial layer, mucin and defensin secretion, and by proxy, the microflora. If the balance is disturbed, intestinal permeability may occur which leads to increased activation of the immune system. igA = Immune globulin A; TLR = Toll like receptor; SCFA = Short chain fatty acids. Adapted from (Natividad and Verdu, 2013), with permission.

4.5. Immune activation

Many studies support the presence of low level mucosal inflammation in IBS-C (Chadwick et al., 2002; Dunlop et al., 2003; Ford and Talley, 2011; Gwee et al., 2003), with slight increases in T-cells (Spiller et al., 2000; Walker et al., 2009), recruited macrophages (Spiller et al., 2000) and mast cell invasion (Barbara et al., 2007; Cremon et al., 2009; O'Sullivan et al., 2000; Piche et al., 2008; Walker et al., 2009; Wang et al., 2004; Weston et al., 1993) (Figure 3). In people with IBS, the mucosal metabolism shows a shift towards inflammation (Kajander et al., 2009), and so does the cytokine-profile (Dinan et al., 2008; Macsharry et al., 2008; Walker et al., 2011). Cytokines are secreted in response to immune cell activation via pathogen-associated molecular pattern receptors, also called toll-like receptors (TLR). Mucosal and submucosal neurons (Barajon et al., 2009; Rumio et al., 2006) and mast cells express a variety of TLRs (Abreu et al., 2005). Mast cells interact with bacteria, and, depending on which TLR is activated (Varadaradjalou et al., 2003), may release a different set of cytokines and antimicrobials (McCurdy et al., 2003; McKernan et al., 2011; Mrabet-Dahbi et al., 2009). Pathogenic bacteria and their components seem to elicit mainly pro-inflammatory responses (Dietrich et al., 2010), while other bacteria are able to suppress mast cell degranulation by TLR signaling (Kasakura et al., 2009), which may contribute to the positive effects of probiotics (O'Mahony et al., 2005). The regulation of TLR expression is still unclear, but seems to be affected by cytokines (Yang et al., 2010), and also by neurotransmitters like substance P (Tancowny et al., 2010), reflecting the involvement of the ENS in modulation of the immune system (Akbar et al., 2008).

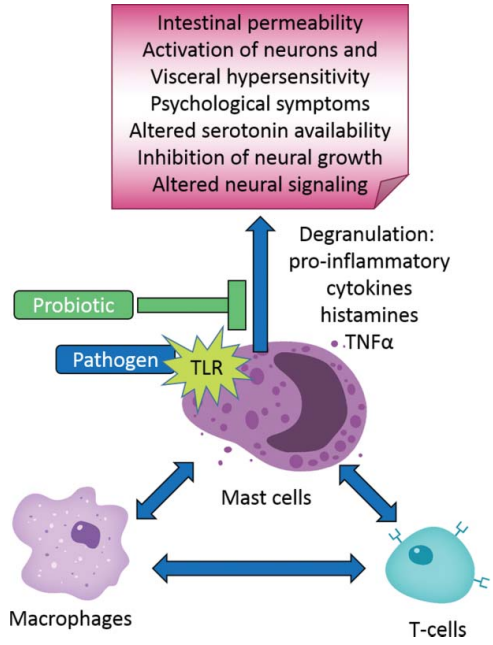

Figure 3. The effects of mast cell activation in IBS. For detailed description see section 4.5. TLR = Toll like receptor.

Altered TLR expression has been observed in IBS (Brint et al., 2011).

The low level of inflammation may have various effects on the gastrointestinal system. The released mediators like histamine and TNFα increase intestinal permeability (Cario et al., 1999; McKay and Singh, 1997), and activate enteric neurons (Barbara et al., 2007; Buhner et al., 2009), leading to visceral hypersensitivity (Barbara et al., 2004; Cenac et al., 2007; Coelho et al., 1998). In addition, TNFα may be responsible for psychological symptoms in IBS-C (Simen et al., 2006; Yamada et al., 2000), and modulate serotonin availability if present at chronically low levels (Anisman et al., 2003; Simen et al., 2006), but not at high doses (Connor et al., 1998; Hayley et al., 1999). Moreover, TNFα may inhibit neural growth (Monje et al., 2003; Santarelli et al., 2003), while mast cell nerve growth factor may increase it (Dothel et al., 2015), leading to altered neural signaling.

4.6. Altered microflora

The interactions between microflora and host are symbiotic in nature. The host shapes the microflora by food and fiber intake, and the microflora modulates host immune responses, metabolism, and the gastrointestinal system (Macfarlane and Macfarlane, 1997; Natividad and Verdu, 2013; Ostaff et al., 2013; Salonen et al., 2010; Sassone-Corsi and Raffatellu, 2015). Differences in the microflora of adults with constipation and IBS-C have been reported, with an increase in *Firmicutes* and a decrease in *Bacteroides* and *Bifidobacteria* (Jeffery et al., 2012; Kassinen et al., 2007; Parkes et al., 2012; Rajilic-Stojanovic et al., 2011). The changes in the flora may be causative (Mendall and Kumar, 1998; Wang et al., 2004), but also mediative, since both antibiotics (Pimentel et al., 2011) and probiotics (Brenner et al., 2009; Moayyedi et al., 2010) seem to relieve some of the symptoms. In addition, the attempt to alter the microflora and reduce gastrointestinal symptoms via dietary changes, especially by reducing fermentable nutrients (FODMAPs), has also shown potential (Bohn et al., 2015; Halmos et al., 2014; Moayyedi et al., 2010) (see section 6.2: FODMAPs).

How the microflora may affect gastrointestinal processes is complex. A methanogenic flora is correlated with slow transit (Attaluri et al., 2010). The manipulation of methanogenic flora is therefore a potential option to address specific aspects of colonic motility (Sahakian et al., 2010). Kim et al. (2012) identified *Methanobrevibacter smithii* as the principal methanogen in patients with IBS-C with methane on breath testing. The number and proportion of *M. smithii* in stool correlates well with the level of breath methane (Kim et al., 2012). Methane present on breath testing is significantly associated with constipation in both IBS and functional constipation (Kunkel et al., 2011). Other bacteria in the human GI tract, such as certain *Clostridium* and *Bacteroides* species are also capable of producing methane (McKay et al., 1982). The degree of breath methane production in IBS correlates with the severity of constipation (Chatterjee et al., 2007). The complex interrelationship of microflora was further observed by Robert and Bernalier-Donadille (2003) who found that the structure and activity of colonic cellulolytic microbial community differed significantly between methane and non-methane producing individuals. They suggested that isolates of hydrogen-producing fibrolytic bacteria such as *Ruminococcus* and *Enterococcus* could be essential for the development of methanogens in the colon (Robert and Bernalier-Donadille, 2003).

The microflora is able to modulate host immune responses by activation of TLRs on immune cells (Brint et al., 2011). However, modulation of gastrointestinal processes by the microflora also includes alteration of bile acid composition and SCFA production (Camilleri, 2012). SCFAs like propionate, butyrate and acetate, are able to induce peristaltic contractions by stimulation of EC-cells and secretion of serotonin (Fukumoto et al., 2003; Kamath et al., 1987; Mitsui et al., 2005). SCFAs can also regulate water retention by induction of ion transport and release of peptide YY (Karaki and Kuwahara, 2011; Karaki et al., 2006). The change in SCFA patterns may also be behind the symptom relief induced by a low FODMAP diet (Ong et al., 2010; Shepherd et al., 2008).

5. Review of the nutritional composition of green kiwifruit

The green kiwifruit (*Actinidia deliciosa* var. Hayward) has been extensively characterized. A comprehensive report was conducted by Zespri Group Limited in 2005 (McGhie et al., 2005), and many of the compounds have been discussed in detail elsewhere (Boland and Moughan, 2013). Since an in depth analysis of the compounds found in green kiwifruit is beyond the scope of this review, the following section focuses on compounds found in green kiwifruit thought to be most relevant to their effects on the human gastrointestinal tract.

5.1. Carbohydrates, sugar alcohols, and fiber

The green kiwifruit is one of the most nutrient dense commonly consumed fruit (Boland, 2013; Ferguson and Ferguson, 2003; La Chance, 1997; McGhie et al., 2005), when its nutrients

Table 1. Selected macro- and micronutrients of green kiwifruit.

Nutrient	Unit	Value per 100 g edible flesh of green kiwifruit	% of Daily Value/ Recommended Daily Intake
Water	g	83.07	—
Protein	g	1.14	0.02
Actinidin[1,2]	mg	80-430	—
Kiwellin[2]	mg	44	—
Lipids	g	0.52	0.008
Sugars, total	g	8.99	—
Glucose	g	4.11	—
Fructose	g	4.35	—
Fiber	g	3	12
Calcium	mg	34	3.4
Magnesium	mg	17	4.25
Potassium	mg	312	8.9
Sodium	mg	3	0.1
Vitamin C	mg	92.7	154
Vitamin E, total	mg	1.49	10
Vitamin K	μg	40.3	50
beta-Carotene	μg	52	—
Lutein & Zeaxanthin	μg	122	—

Data based on UDSA National Nutrient Database for Standard Reference (US Department of Agriculture, 2016), unless stated otherwise.
[1]Data from Nishiyama (2007);
[2]Data from Ciardiello et al. (2009). For a complete overview on kiwifruit micro- and macronutrient content, see McGhie et al. (2005), Boland (2013).

are compared as a function of energy value. The favorable nutrient density is mainly driven by its high vitamin C content (Taylor et al., 2004) (Table 1). Due to the high water and fiber content, the green kiwifruit can be named a low-caloric food (Henare et al., 2012). The sugar profile of kiwifruit is valuable for consumers following the low FODMAP (see Section 6.2: FODMAPs) diet: it consists of nearly equal amounts of glucose and fructose, and a low level of sucrose (Nishiyama, 2007), which is favorable in cases of fructose malabsorption (Latulippe and Skoog, 2011). The fiber content of green kiwifruit (3g/100 g edible flesh) is comparable to that of other fruit (US Department of Agriculture, 2016), and is approximately 2/3 insoluble and 1/3 soluble (Carnachan et al., 2012). The insoluble fiber consist of hemicelluloses, cellulose and pectin, and the soluble fiber is mainly a mixture of pectic polysaccharides (Carnachan et al., 2012). However, kiwifruit fiber has some unique properties. Its capacity of swelling, defined as the volume fiber has in water after passively settling (Robertson et al., 2000), is more than six times higher than that of apple fiber, and one and a half times higher than psyllium after freeze-drying (Sims and Monro, 2013). Kiwifruit fiber has also an impressive higher water retention capacity (Mishra and Monro, 2012; Sims and Monro, 2013), which is the amount of water that is bound to insoluble fiber and is not separated from fiber by centrifugation (Robertson et al., 2000). These properties affect the dynamics of nutrient absorption, reducing mixing in the bowel and diffusion (Mishra and Monro, 2012; Monro, 2013). Kiwifruit fiber may add to fecal bulking as part of a balanced diet (Sims and Monro, 2013), however it is also completely fermentable by the microflora and therefore may have a significant role in modulation of the microflora (Rosendale et al., 2012)

5.2. Proteins, amino acids and peptides

While green kiwifruit are not a significant source of protein (US Department of Agriculture, 2016), they do contain unique proteins and amino acids interesting to health. These minor proteins may be responsible for, or at least contribute to, the observed effects of green kiwifruit consumption on constipation and IBS-C.

The predominant protein in green kiwifruit is actinidin (Boland, 2013). Other identified proteins are kiwellin and its peptides KiTH (Boland, 2013) and kissper (Ciardiello et al., 2008), and a thaumatin-like protein (Wurms et al., 1999). Actinidin is a cysteine protease with proteolytic activity and structural homology similar to that of papain (McDowall, 1973; Pickersgill et al., 1989), albeit with a more narrow specificity for its substrates (Chalabi et al., 2014). Actinidin activity is observed across a wide pH range of 3-8, depending on the substrate (Arcus, 1959; Boland and Hardman, 1973; Nishiyama, 2007), and shows some resistance to pepsin degradation in its proteolytic active form (Grozdanovic et al., 2014), reaching the colon. Actinidin cleaves the protein kiwellin into kissper and KiTH (Ciardiello et al., 2008; Tuppo et al., 2008). The biological function of kiwellin and KiTH are poorly understood. Kissper, however, seems to be able to form ion-channel like pores by integrating itself into phospholipid membranes (Ciardiello et al., 2008; Meleleo et al., 2012), and may have anti-inflammatory properties (Ciacci et al., 2014). The kiwifruit thaumatin-like protein appears to have some antifungal activity (Wang and Ng, 2002). A cysteine-proteinase inhibitor (CPI) has also been isolated, which shows both antifungal and antibacterial properties (Popovic et al., 2013; Popovic et al., 2012). Other enzymes in green kiwifruit are linked to ripening, sugar metabolism, and growth (Boland, 2013), and are probably not involved in the effect of green kiwifruit on abdominal discomfort.

Green kiwifruit protein is rich in the amino acids glutathione, arginine and γ-amino butyric acid (GABA), and modest in serotonin, tryptophan and tryptamine (Table 2) (Herraiz and Galisteo, 2003; MacRae and Redgwell, 1992; Witschi et al., 1992). Glutathione is a tripeptide that acts as an effective antioxidant. While it maintains the activity of vitamin C and vitamin E in green kiwifruit, glutathione may not survive digestion in the small intestine (Hagen et al., 1990; Witschi et al., 1992). Arginine is a conditional essential amino acid, and GABA is a neurotransmitter which lowers excitation of neurons. Serotonin is synthesized from tryptophan, an essential amino acid, and tryptamine is a serotonin receptor agonist. Since their

Table 2. Minor green kiwifruit components of potential interest.

Nutrient	Unit	Value per 100 g edible flesh of green kiwifruit
Flavonoids	g	4.6
Chlorogenic acid[2]	mg/L juice	0.68
Asparagine[3]	mg	0.17
Aginine & GABA[3]	mg	7.7
Glutamine[3]	mg	1.3
Glutathione[4]	mg	22.5
Serotonin[5]	mg	0.6
Tryptamine[5]	mg	0.9
Tryptophan[5]	mg	0.7

Data based on UDSA National Nutrient Database for Standard Reference (US Department of Agriculture, 2016), unless stated otherwise.
[2]Data from Dawes and Keene (1999).
[3]Data from MacRae *et al.* (MacRae and Redgwell, 1992);
[4]Data from Witschi *et al.* (Witschi et al., 1992);
[5]Data from Herraiz *et al.* (Herraiz and Galisteo, 2003); For a complete overview on minor components of kiwifruit, see McGhie et al. (2005), Boland (2013).

concentrations in green kiwifruit are lower than in other food, for example spinach (163 mg/g arginine (US Department of Agriculture, 2016), 43 μg/g GABA (Oh, 2003)), egg whites (125 mg/g tryptophan) (US Department of Agriculture, 2016) and black walnuts (300 μg/g serotonin) (Feldman and Lee, 1985), it is unlikely that these amino acids play a major role in the effects of kiwifruit consumption on constipation or IBS-C.

5.3. Vitamins and minerals

The high vitamin C content of green kiwifruit (Table 1) and its antioxidant properties is one of its notable features, and no loss of vitamin C has been observed during storage (Tavarini et al., 2008). Green kiwifruit also contain high levels of vitamin E (US Department of Agriculture, 2016). Multiple isomeric forms of vitamin E are present in green kiwifruit; α-tocopherol, δ-tocopherol, γ-tocopherol, γ-tocotrienol, δ-tocotrienol, and a recently discovered form, δ-tocomonoenol (Fiorentino et al., 2009; Van Hoed et al., 2009). Vitamin E has effects on immune cells (Devaraj et al., 2001; Devaraj et al., 1996) and endothelial cells (Boscoboinik et al., 1991; Chan et al., 1998), which may all be attributed to its main function as an antioxidant (Traber and Atkinson, 2007). Generally, the presence of vitamin E alters intracellular signaling which uses oxidative species (Traber and Atkinson, 2007), resulting in changed expression of protease-activated receptors (PAR, see section 6.1: Cysteine proteases in fruits) and secretion of pro-inflammatory cytokines, and thus may even modulate mast cell activation and degranulation (Han et al., 2012). Vitamin E is a fat soluble compound and was originally thought to be located completely in the kiwifruit seeds (Ferguson and Ferguson, 2003), which are rarely digested. However, the location of vitamin E being limited to the seeds of green kiwifruit is disputable (McGhie, 2013), with recent research suggesting it is also present in the flesh, and thus could have a higher bioavailability than expected (see also section 8.6: Modulation of inflammation by vitamins). Another vitamin in green kiwifruit is folate (Ferguson and Ferguson, 2003) but its content is relatively low compared to other fruits, for example papayas (US Department of Agriculture, 2016). However, folate is known to be involved in DNA synthesis and repair, and brain functions, and recent studies have linked folate to serotonin and cholinergic receptors (Brocardo et al., 2008). Further, green kiwifruit have a high concentration of potassium (Boland, 2013). Potassium is involved in many biological processes such as the resting membrane potential of all cells, and water retention in the colon.

5.4. Organic acids and oxalates

Besides vitamin C, green kiwifruit contains a range of other organic acids including citric acid, oxalic acid, malic acid and quinic acid (Boland, 2013; Nishiyama, 2007). Oxalic acid is predominantly present in the form of calcium oxalate monohydrate crystals, called raphides (see section 8.4: Effect of raphides). Raphides are insoluble in water, but soluble at low pH (Hagler and Herman, 1973). The raphides are known to irritate the oral mucosa is some individuals (Perera et al., 1990), and may irritate the gastrointestinal mucosa, but it is unclear if raphides can escape solubilization in the stomach. While oxalates in large quantities are known to have a negative impact on health (Noonan and Savage, 1999), the small quantity found in green kiwifruit is unlikely to elicit negative responses (Nishiyama, 2007). Dietary oxalate intake may even have benefits by modulating the microflora (Allison et al., 1986; Allison et al., 1985; Campieri et al., 2001; Miller and Dearing, 2013; Turroni et al., 2010; Turroni et al., 2007). Oxalic acid is a natural product of vitamin C degradation (Keates et al., 2000; Kostman et al., 2001; Parsons et al., 2011).

5.5. Carotenoids, chlorophyll and phenols

The carotenoids present in green kiwifruit include lutein, violaxanthin and β-carotene, and are responsible for the underlying yellow color (Cano, 1991; McGhie and Ainge, 2002; Nishiyama et al., 2005). Carotenoids are known to be potent antioxidants, and are highly bioavailable in kiwifruit (O'Connell et al., 2007). The color of green kiwifruit is caused by the presence of chlorophyll (McGhie and Ainge, 2002). Another interesting group is phenols, including epicatechin, caffeic and ferrulic acid, and quercetins (Arts et al., 2000; Brat et al., 2006; Dawes and Keene, 1999) (see section 6.3: Polyphenolic compounds). While the phenolic content is negligible when compared to other fruits (Mattila et al., 2006), it has been observed that kiwifruit phenols are metabolized by the microflora in rats (Lin et al., 2011).

Finally, it is likely that a range of minor but potentially bioactive compounds present in green kiwifruit are yet to be identified (McGhie, 2013).

6. Common fruit and vegetable compounds with known influence on gastrointestinal function

From a clinical perspective, symptom management of constipation and IBS-C is the basis of current therapeutic approaches. The American Gastroenterological Association suggests a step-by-step approach for treatment of constipation (American Gastroenterological et al., 2013), changing the management regimen only when the symptoms are not relieved. The recommended treatment options start with increased fiber intake and an osmotic agent like magnesium salts, then a stimulant laxative like bisacodyl, followed by use of a chloride channel activator like lubiprostone, or a serotonin receptor agonist like tegaserod, to increase water content and motility. Other medications include anti-spasmodics (meveberine) and peppermint oil. However, people, particularly those at the less severe end of the severity spectrum, prefer more natural options and frequently turn to traditional remedies suitable for long term use. In general, traditional food-based options for the relief of constipation include fruits like pineapple, apples, or prunes. In many cases the underlying mechanisms have not been determined, and whether these foods have any effect on constipation is yet to be proven. Here we discuss a variety of foods and compounds that have been demonstrated to affect the gastrointestinal tract.

6.1. Cysteine proteases in fruits

Actinidin is not the only cysteine protease in fruit. Bromelain, papain, and ficin are found in pineapple, papaya, and figs, respectively, all of which are used as traditional remedies against

constipation (Lim, 2012a, b; Nwankudu et al., 2014; Stettler, 1944; Thanaraj and Terry, 2011; Younger, 1895). Fresh pineapple juice increased the contraction of rabbit jejunum *ex vivo* (Nwankudu et al., 2014), which suggest that the active component is water soluble. Bromelain, which is water soluble, may undergo partial digestion in the stomach, but some of it is still proteolytically active in the small intestine in rats (Hale, 2004). The residual activity is able to remove molecules from epithelial cells and macrophages. *In vitro*, bromelain limited extracellular regulated kinase activity and expression of pro-inflammatory cytokines in T-cells and epithelial cells (Engwerda et al., 2001; Mynott et al., 2002; Mynott et al., 1999) by proteolytic cleavage of specific cell surface molecules. When colon biopsies were treated with bromelain *in vitro*, levels of pro-inflammatory cytokines were reduced (Onken et al., 2008). This included interferon γ, and TNF-α, but not IL1-β or IL6. In IL10-deficient mice, long term supplementation with pineapple juice or bromelain decreased histological markers of inflammation (Hale et al., 2010; Hale et al., 2005), which is dependent on its proteolytic activity. In addition, bromelain is also absorbed in the human gastrointestinal tract without loss of its proteolytic activity (Castell et al., 1997; Chobotova et al., 2010), and may cause its effects systemically. Bromelain also decreases bradykinin (Lotz-Winter, 1990; Suda et al., 1984) by proteolysis. Bradykinin increases COX2 activity and prostacyclin production (Sharma, 1988), and stimulates NO formation in epithelial cells (Palmer et al., 1988). Whilst it has been observed that bradykinin is able to decrease colonic motility in humans (Murrell and Deller, 1967), most studies suggest bradykinin is likely to increase gastrointestinal motility (Fasth and Hulten, 1972; Sharma, 1988).

In a constipation rat model, supplementation with fig paste increased fecal output and water content, and decreased transit time (Lee et al., 2012a). Similar results with decreased transit time were found when fig paste was given to beagles with feed-induced constipation (Oh et al., 2011). In both studies, it was suggested that the motility effects were caused by the fiber content of the figs. It has also been reported that methanol fig extracts enhances motility in various animals at low concentrations, but decrease motility at high concentrations (Amos et al., 2001). In rabbits, ethanolic extracts of figs showed spasmolytic effects in relation to K^+_{ATP}-channel activation (Gilani et al., 2008). Fig juice, when given longer than 2 weeks, improved colonic transit time in humans with functional constipation (Kim et al., 2010).

While green papaya is traditionally used as a mild laxative, few studies on its mechanism of action (Akah et al., 1997; Nwankudu et al., 2014) or on its effectiveness exist (Muss et al., 2013). Nwankudu et al. (2014) found that application of papaya juice reduced the contractions of rabbit jejunum *ex vivo*, and hypothesized that the fiber content of papaya may be responsible for the laxative effect. Muss et al. (2013) noted significant relief from constipation in adults when given a preparation from papaya in comparison to placebo. Akah et al. (1997) reported an increase in peristalsis and fecal water content in rats when supplemented with an aqueous extract from papaya roots, which is likely to be completely different from an extract of the fruit. Neither study identified the compounds potentially responsible for these effects.

The common component in figs, papaya and pineapple are the cysteine proteases. Epithelial cells express protease activated receptors, or PAR (Buresi et al., 2001; Kouzaki et al., 2009), as well as T-cells and basophils (Liang et al., 2012). These receptors can be activated by cysteine proteases like papain to elicit a pro-inflammatory cytokine response. PAR are also found in the ileum (Corvera et al., 1999) and sensory neurons, where they are involved in neurogenic inflammation and pain signaling (Saito and Bunnett, 2005), but also in ion transport (Buresi et al., 2001). PAR are also activated by mast-cell tryptase (Vergnolle et al., 2001), which can be of importance in IBS-C. Since proteolytic activation of PAR2 is also able to modulate an anti-inflammatory response to colitis in mice (Fiorucci et al., 2001), while activation of PAR4 decreases colonic hypersensitivity (Auge et al., 2009), modulation of intestinal transit, pain and ion transport by plant cysteine proteases is a possibility that warrants further research.

6.2. FODMAPs

Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAPs) are food compounds that are able to cause bloating, gas, constipation or diarrhea in susceptible individuals. FODMAPS include, for example, fiber like fructo- and galacto-oligosaccharides, lactose (milk sugar), fructose, and sugar alcohols like sorbitol and xylitol. FODMAPs may cause abdominal discomfort by fermentation by the microflora, which can increase gas production. In this case, reduction of FODMAPS may help with symptom management (Bohn et al., 2015; Halmos et al., 2014; Ong et al., 2010; Rao et al., 2015). In people with malabsorption, or at a high concentration, FODMAPs may overwhelm digestive enzymes or transport in the small intestine, where they can act as osmotic substances. Osmotic substances draw water into the colon (Ellis and Krantz Jr, 1941), which can be used to relieve constipation. Common examples include lactulose, sorbitol, lactose, apple and pear juice (Heyman and Committee on Nutrition, 2006; Hoekstra et al., 1993; Schiller, 2001; Wesselius-De Casparis et al., 1968). Prunes, recognized by the European Union as beneficial for the relief of constipation and normalization of bowel habit (European Commission, 2013), are dried plums that contain high concentrations of sorbitol (Stacewicz-Sapuntzakis et al., 2001). The sorbitol, together with dietary fiber, contributes to the effectiveness of prunes in the management of constipation. Prunes also contain 1.4-2.2% oligosaccharides in their dry matter (Dikeman et al., 2004), which is another FODMAP. Kiwifruit, in comparison, contain neither sorbitol nor oligosaccharides (McGhie et al., 2005; Sims and Monro, 2013), making kiwifruit a low FODMAP-diet friendly fruit. A recent pilot study demonstrated that the consumption of two green kiwifruit is not associated with clinically significant evidence of colonic fermentation as shown by hydrogen and methane on breath testing (Chen et al., 2017), thus lending support for the low FODMAP status for kiwifruit.

6.3. Polyphenolic compounds

Bile acids can increase motility by reduction of electrolyte and water resorption, softening fecal matter and increasing frequency (Hepner and Hofmann, 1973). Artichoke leaf extract stimulates bile production and secretion (Kraft, 1997; Matuschowski et al., 1996; Rodriguez et al., 2002), and inhibits

cholesterol synthesis (Gebhardt, 2000). The inhibitory effect has been appointed to the flavones luteolin and cynaroside, a glucoside version of luteolin (Gebhardt, 2000). In a small German study, chlorogenic acid and cynarin, a dicaffeic acid derivative, were tested for their effects on bile flux in rat livers (Matuschowski et al., 2005). Cynarin increased bile secretion significantly, and so did chlorogenic acid (13.9 mg), but to a lesser degree. It was also shown that secretion of bile was prominently increased by the phenolic content of artichoke leaf extract. In a small study from Uruguay the polyphenolic compounds found in the mate species *Ilex brevicuspis* also increased bile flux in rats (Filip and Ferraro, 2003). Furthermore, the polyphenolic extract also increased gastrointestinal transit in this study. Caffeic acid derivatives and chlorogenic acid derivatives are also present in kiwifruit, albeit at lower levels (Dawes and Keene, 1999) (Table 2). Since bile acids decrease gastrointestinal transit time (Rao et al., 2010), the phenolic content of green kiwifruit may contribute to its effect on transit time. However, the dose-dependent nature of the relationship between chlorogenic acid and bile flux in humans is unknown, the phenolic content of green kiwifruit is not well characterized, and the effect of green kiwifruit on bile flux has not been studied so far.

Many scientifically-backed treatments for constipation involve polyphenols such as anthraquinone derivatives and diphenyls. The most used anthraquinone derivatives are aloin and aloe-emodin from aloe vera, sennosides from senna, rhein from rhubarb, and cascara sagrada. Anthraquinone derivatives are highly effective stimulant laxatives (Schiller, 2001), which elude digestion and get processed into their active forms by the microfora (Van Os, 1976). They inhibit electrolyte absorption and increase the fluid in the colon (Ewe, 1980). However, they may also increase motility by release of mediators after damage to mucosal cells (Gorkom and Vries, 1999). Rhein, for example, is present in kiwifruit roots (Chen et al., 2012), but to date no anthraquinone has been identified in the flesh. It is therefore unlikely that kiwifruit alleviate constipation and IBS-C through this mechanism.

Diphenyls such as bisacodyl have also shown effectiveness as stimulant laxatives (Schiller, 2001). Diphenyl isatin (Baum et al., 1951) for example is a naturally occurring diphenyl present in prunes, and may add to their laxative effect. Diphenyls act on the colon by increasing prostaglandin E2 (PGE2) production in intestinal epithelial cells, inhibiting of the Na^+-K^+-ATPase (Rachmilewitz et al., 1980; Schreiner et al., 1980), and probably activating macrophages, which produce the pro-inflammatory cytokines TNF-α, Il-1β, IL-6, and PGE2 (Ikarashi et al., 2011). In response to PGE2, epithelium cells increase expression of aquaporin 3, limiting water absorption by the colon. However, diphenyl isaten has never been isolated from plants, and the effects of prunes on aquaporins have not been studied.

7. Summary of published and unpublished mechanistic work on green kiwifruit

7.1. Influence of kiwifruit fiber on ileal digestibility, water retention, and bulking

In pigs fed with semisynthetic diets containing both crushed, fresh green, yellow kiwifruit, and freeze dried kiwifruit (Henare and Rutherfurd, 2013), decreased digestibility and uptake of protein and lipids in the small intestine was reported for all kiwifruit preparations (Henare and Rutherfurd, 2013; Henare et al., 2012). Soluble fiber was highly digested after passage through the small intestine, whereas insoluble fiber was not (Henare and Rutherfurd, 2013). The oxalate-soluble pectin of kiwifruit had been fully absorbed in the small intestine, whereas the pectic fractions were completely fermented in the colon. Overall, feeding kiwifruit increased water retention and fecal bulking, and decreased transit time in pigs (Henare and Rutherfurd, 2013; Montoya et al., 2014). These results are aligned with the observations in humans (Chan et al., 2007; Chang et al., 2010; Rush et al., 2002).

7.2. Influence of kiwifruit fiber on microflora

In humans, the intake of freeze-dried green kiwifruit rapidly increased *Lactobacillus* and *Bifidobacteria* species, and lead to an insignificant downward trend in *Clostridia* and *Bacteroides* (Lee et al., 2012b). The effect was transient in nature (Lee et al., 2012b). An *in vitro* fermentation model supports these findings (Parkar et al., 2012), as well as an animal model using pigs fed with kiwifruit fiber (Han et al., 2011). However, in rats fed kiwifruit, no difference in *Lactobacillus* and *Bifidobacteria* species were observed compared to controls, but enhanced production of SCFA and an increase in *Lachnospiracea* were reported (Paturi et al., 2014). The enhanced production of SCFA was previously observed in an *in vitro* model, and correlated with an increase in defensin release (Bentley-Hewitt et al., 2012). No changes in defensin release were observed in the animal model (Paturi et al., 2014). The shifts in microflora composition following consumption of kiwifruit (Rosendale et al., 2012) may potentially contribute to a reduction or suppression of methanogenic bacteria, which can influence colonic motility (Kim et al., 2012; Kunkel et al., 2011), providing putative evidence for the apparent effective changes in transit in constipated but not non-constipated individuals.

7.3. Influence of kiwifruit fiber on gastrointestinal transit time

While kiwifruit fiber provides bulking, it may not be directly responsible for the observed decrease in gastrointestinal transit time (Chan et al., 2007; Drummond and Gearry, 2013; Henare and Rutherfurd, 2013; Montoya et al., 2011; Montoya et al., 2014). In addition, fiber seems to behave different in the whole fruit versus extracted fiber (Drummond and Gearry, 2013). In an older study, a water-soluble fraction alone (mostly actinidin and mucilage) was enough to decrease transit time in rats, while not increasing bulk (L. Ferguson, unpublished results, R. Schroeder, unpublished results). More recently, the decrease in gastrointestinal transit time was linked to actinidin (Montoya et al., 2014). In this study, gold kiwifruit, which contains a negligible amount of actinidin, was used as a negative control, as well as green kiwifruit where the actinidin was chemically inactivated (Montoya et al., 2014).

7.4. Enhancement of protein digestion and gastric emptying by actinidin

In rats, the addition of freeze-dried green kiwifruit to the feed increased digestion of beef muscle, gluten, and soy protein isolate in the stomach (Rutherfurd et al., 2011). This effect was attributed to actinidin. In a study using pigs, digestion of beef muscle was increased while gastric transit time was decreased with fresh green kiwifruit when actinidin was active but not when actinidin was chemically inactivated (Montoya et al., 2014). Further, gastric emptying was decreased with gold kiwifruit, but not with gold kiwifruit when actinidin was added (positive control). This is in line with a study which measured gastric empting in rats with magnetic resonance spectroscopy (Montoya et al., 2011), and another study in pigs fed with semisynthetic diets containing both crushed, fresh green and yellow kiwifruit and freeze dried green kiwifruit (Henare and Rutherfurd, 2013). The rate of gastric emptying is a result largely of the energy and nutrient density of the consumed food (Little et al., 2007; Marciani et al., 2001). Fat, glucose, and amino acids in the lumen of the small intestine lead to secretion of CCK, which reduces gastric emptying and pancreatic secretion to increase absorption. It was proposed that the increase of gastric emptying was a result of an increased level of protein hydrolysis, or increased amino acid uptake into the cells (Montoya et al., 2014). In an unpublished human study, the addition of kiwifruit to a high protein meal (steak) significantly reduced abdominal discomfort and reduced bloating (R. Gearry, L. Drummond, unpublished results).

7.5. Effects of kiwifruit on the gastrointestinal barrier

Research concerning the interaction of kiwifruit and the mucus layer is limited (Moughan et al., 2013). In pigs, increasing amounts of kiwifruit in their diet correlated with increased mucin production in the stomach and duodenum, and increased mRNA expression for muc1 in duodenal tissue (S. Henare, unpublished data) (Moughan et al., 2013). In rats, long term feeding of kiwifruit increased expression of muc2 and muc3 genes (Paturi et al., 2014). Interestingly, pretreatments with kiwifruit extracts also reduced intestinal permeability in response to TNF-α and interferon γ in cultured cells (unpublished data, see (Skinner et al., 2013)). However, whether this effect is attributable to fiber, a water-soluble compound, or even to raphides, is unknown so far.

7.6. Modulation of inflammation

Kissper is resistant to protein digestion with pepsin, trypsin and chymotrypsin (Ciacci et al., 2014), and is therefore potentially active in the gastrointestinal tract. Pre-treatment with kissper was reported to inhibit redox state disruption and intracellular calcium increase in a colonic epithelial cell line and ex-vivo colonic cells of patients with Crohn's disease during a challenge with *Escherichia coli* (Ciacci et al., 2014). It also limited NF-κB activation by reducing nuclear p65 localization and subsequent TNF-α release. The expression of transglutaminase 2 was inhibited, while the release of the anti-inflammatory cytokine TGF-β1 was increased in this study. How it was able to elicit these observed effects was not determined.

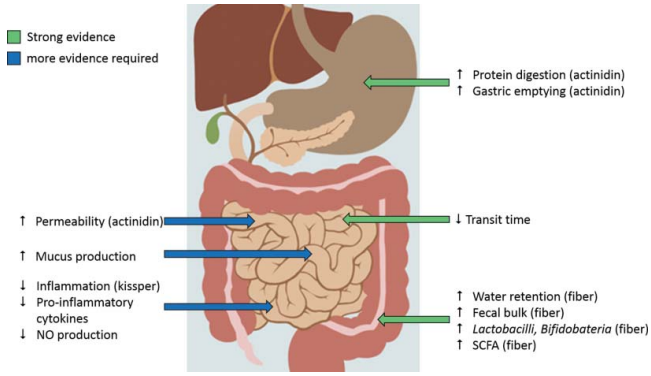

Figure 4. Summary of effects of kiwifruit on the gastrointestinal system. Some of the mechanisms described in the text have been extensively studied in different systems, while others have been described only in one system and have not yet been evaluated in other systems.

In another study, the addition of aquaeous and ethyl acetate kiwifruit extracts to cultured murine macrophages reduced LPS-induced NO production, and pro-inflammatory cytokine secretion (Edmunds et al., 2011). Kiwifruit extracts also inhibited cytokine production in colon epithelial cells, even in cells of IL10 knockout mice. It was concluded that IL10 was not necessary for the anti-inflammatory response, and suggested to involve TLR4 signaling. However, the active components within the extracts were not characterized. Any potential differences in inhibition levels related to higher concentrations of active components, or different components in the ethyl acetate extracts, were not evaluated. Further, the observed anti-inflammatory effect of the extracts *in vitro* was absent in an *in vivo* mouse model for inflammatory bowel disease, where only mild changes in adaptive immune signaling were observed (Edmunds et al., 2012). In another study involving mice, kiwifruit extracts significantly enhanced specific intestinal mucosal responses to vaccines (Shu et al., 2008).

For an overview and rating of the discussed mechanisms see Figure 4.

8. Other possible mechanisms based on nutritional analysis of green kiwifruit

8.1. Kiwifruit cysteine protease inhibitor (CPI)

Fecal cysteine proteases have been reported to be elevated in IBS-C, causing degradation of occludin, a tight junction protein, and pain (Annahazi et al., 2013). It may be that kiwifruit CPI is able to inhibit fecal cysteine proteases and increase transit time by normalizing gastrointestinal function. Purified CPI limited the growth of two typical plant pathogenic fungi at a micromolar level (Popovic et al., 2012). If CPI is able to survive digestion and uptake, it could, in theory, influence human microflora. However, the high concentration of actinidin within green kiwifruit makes this questionable.

8.2. Other putative effects of actinidin

It is possible that actinidin activates PAR2 and PAR4 by proteolysis and modulates pain and inflammation, or increases secretion of chloride and water by activation of PAR1. It is also

probable that proteolysis of bradykinin modulates motility (see section 6.1: Cysteine proteases in fruits)

8.3. Effects of phenols and polyphenols

It has been shown that a diet rich in polyphenols is able to modulate immune functions (Bub et al., 2003). This includes quercetin (Nieman et al., 2007a; Nieman et al., 2007b), and carotenoids (Watzl et al., 2003). The phenolic compounds in kiwifruit have been shown to possess antimicrobial activity (Ansell et al., 2013; Molan et al., 2008), and quercetin, which is present in kiwifruit, enhances inhibition of pathogenic adhesion to epithelial cells by vitamin C *in vitro* (Ansell et al., 2013). Polyphenols are also able to bind to T-cell receptors directly to elicit a cytokine response (Holderness et al., 2008; Jutila et al., 2008). In addition, the phenolic content of green kiwifruit may increase aquaporins in a manner similar to diphenyls like bisacodyl, or chlorogenic acids present in green kiwifruit may increase bile secretion. The phenolic content of green kiwifruit should be further characterized.

8.4. Effects of raphides

Raphides are insoluble in water, but soluble at a pH < 3 (Hagler and Herman, 1973). However, breakdown of the crystals may be slow and incomplete under gastric conditions (Hanes et al., 1999), and may be even more so in green kiwifruit, since the surrounding mucilage of the fruit may protect the raphide crystals. This could mean that they are present in the gastrointestinal tract to either increase mucin production or to interact with the intestinal flora (Allison et al., 1986). Oxalates can be used as an energy source by *Lactobacilli* and *Bifidobacteria* species and increase these populations (Campieri et al., 2001; Hokama et al., 2000; Turroni et al., 2010; Turroni et al., 2007), which are normally low in individuals with IBS-C (Jeffery et al., 2012; Kassinen et al., 2007; Parkes et al., 2012; Rajilic-Stojanovic et al., 2011).

8.5. Ion channel formation by Kissper

As mentioned in section 5.2, kissper may insert itself into membranes and form ion channels (Ciardiello et al., 2008). Since publications on kissper are still limited, pore formation by kissper should be further characterized. If kissper is enriched in gastrointestinal epithelium *in vivo* after ingestion of kiwifruit, motility may be enhanced by increased water secretion into the lumen.

8.6. Modulation of inflammation by vitamins

Low-level inflammation can alter serotonin signaling (see section 4.2: Visceral hypersensitivity and serotonin signaling and section 4.5: Immune activation), slowing down gastrointestinal motility. Normalization of the immune profile may also normalize gastrointestinal function. This change to a more anti-inflammatory environment may be induced by adequate levels of vitamins E and C. Leucocytes, for example, need a higher level of vitamin C to reach saturation than previously assumed, around 100 mg/day (Carr and Frei, 1999; Levine et al., 1996; Levine et al., 2001). Adequate vitamin C levels enhance neutrophil bactericidal activity (Bozonet et al., 2015), and may also be able to influence macrophage and mast cell function. In addition, skin keratinocytes, which are specialized epithelial cells, need vitamin C and E to reduce inflammation caused by UV damage (Fuchs and Kern, 1998). It is therefore likely that intestinal epithelium may also need higher intracellular levels of vitamin C and E to limit inflammation.

Since there are compounds in kiwifruit that are not yet identified, it is possible that some molecules responsible for the observed reduction of transit time remain unknown. It is also likely that some compounds work in synergy to create the observed effects, since many compounds seem to be able to modulate immune cell function, secretion and motility at higher concentrations than the ones observed in kiwifruit.

Table 3. Overview of the putative influence of kiwifruit on bowel habit.

Component	Putative Mode of Action	Potential
Actinidin	Modulation of pain, inflammation, motility and water secretion via PAR activation or TLR signaling	high
Vitamin C and Vitamin E	Modulation of inflammation and epithelial cell function	high
Compounds influencing microflora composition	Direct or indirect influence on colonic motility through modulation of methanogens and methane	high
Kissper	Modulation of inflammation	moderate to high
Actinidin	Modulation of motility and NO production by proteolysis of bradykinin	moderate
Phenolic compounds	Immune modulation, increase of aquaporins and bile secretion	moderate
Kissper	Formation of ion channels in epithelial membranes	moderate
Raphides	Irritation of gastrointestinal mucosa and increased mucus production	moderate
Raphides	Modulation of microflora	moderate
CPI	Inhibition of mast cell serine proteases and change of microflora	low to very low

The author has rated the likelihood of hypothetical mechanisms on the quality and quantity of supporting research, the physiological and pathophysiological mechanisms, and the qualitative as well as quantitative analysis of kiwifruit. Range of likelihood is between very high to very low. CIP = Cysteine protease inhibitory protein; PAR = Protease activated receptor; NO = nitric oxide

Table 4. Future research recommendations.

I. Detection of kissper in intestinal epithelium in animals fed with kiwifruit, and identification of cellular localization
II. Measurement of bile flux in animals; Detection of changes in bile salts in humans after green kiwifruit supplementation
III. Detection of actinidin concentrations and activity in plasma and fecal matter after small bowel passage
IV. Relationship between microflora composition, in particular methanogens, methane production and constipation status
V. Detection of raphides in digesta and measurement of mucus production after raphide application
VI. Measurement of cytokine production in cell culture after addition of purified actinidin to epithelial cells
VII. Assessment of COX2 activity, prostaglandin synthesis, aquaporins and PAR activation in cell culture after supplementation with actinidin and aquaeous green kiwifruit extracts
VIII. Evaluation of mast cell activity and TLR expression in presence of green kiwifruit extract and purified actinidin
IX. Evaluation of intracellular vitamin C content in colonic epithelial cells in animals or humans after supplementation with green kiwifruit
X. Determination of CCK secretion during supplementation with green kiwifruit

For an overview and rating of the discussed putative mechanisms see Table 3. For recommendations for future research see Table 4.

9. Conclusion

Green kiwifruit is a well characterized and highly nutritious fruit that can be recommended as a means to increase abdominal comfort in individuals with constipation and those with constipation-predominant IBS. The effects of green kiwifruit on the gastrointestinal tract are reproducible and substantially documented. The mechanisms behind bulking and water retention induced by kiwifruit fiber are well defined, as well as the digestive effects of actinidin.

This review has identified a number of additional putative mechanisms of kiwifruit action on the gastrointestinal tract that are worthy of further investigation (Table 4). Such mechanisms include, for example, changes in microflora together with potential concomitant shifts in methanogens and methane production, the activation of PARs, the effects on bile flux, the induction of aquaporins, or modulation of mast cell activity.

In summary, green kiwifruit are a valuable complement to a healthy diet, with additional benefits for individuals that are affected by constipation and IBS-C. It is clear that the beneficial gastrointestinal effects of green kiwifruit result from more than just the effects of fiber, they include beneficial changes in gastric and ileal digestion, as well as improved gastrointestinal transit and comfort.

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