Use of Prebiotics for Addressing Gut Dysbiosis and Achieving Healthy Gut–Brain Axis

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Abstract

The bacteria in the gastrointestinal tract which forms the gut microbiome plays a vital role in maintaining body homeostasis and health of the host. Any change in the normal gut microbiome composition and function imposes gut dysbiosis, defined as an imbalance of the bacteria in the gut. The central nervous system (CNS) and the gut microbiome are in constant bidirectional communication involving endocrine, neuronal, and immunological mechanisms forming the gut–brain axis (GBA). Emerging preclinical studies suggest that gut dysbiosis may result in GBA dysfunction leading to neurodegenerative and neurodevelopmental diseases, as well as age-related cognitive decline. Therefore, modulation of gut microbiota composition and functionality offers a promising tool for treating or managing gut dysbiosis and in turn achieving a healthy gut–brain axis. Use of prebiotics is gaining attention as the most robust and safe method of achieving such modulation. Prebiotics refer to non-digestible food ingredients predominately some fermentable carbohydrates that can selectively modulate the composition and/or activity of the microbiota of the gut, thus conferring beneficial physiological effects on the host. The metabolism of prebiotics by the gut microbiome induces changes in the gut barrier integrity and promotes the release of metabolites (mainly SCFAs) contributing to the improvement of host health, particularly in the context of GBA. In this chapter, we discuss the concept of prebiotics, microbiota modulation by prebiotics, and the impact prebiotics on GBA.

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11.1 Introduction

The gut-brain crosstalk has garnered the attention of researchers in the past few decades as studies very clearly indicate the overpowering role of the gut microbiome not only in the modulation and regulation of metabolism and immunity, but also in the functioning of the central nervous system (CNS). The gut microbiome plays a key role in influencing the development and function of the nervous system through its constant bidirectional communication with the CNS (Carabotti et al. 2015; Liu et al. 2019). Microbial metabolites are also known to transmit signals to the brain directly or through the autonomic neurons establishing the gut–brain axis (GBA) (Clapp et al. 2017). Given the enormous sharing of function between host and microbiome, the concept of the holobiont has emerged, which regard eukaryotes as a composite structure in which neither the host nor the microbiome can be considered as functioning independently (Zilber-Rosenberg and Rosenberg 2008). Dysbiosis typically occurs when the microbes that are resident in our gastrointestinal tract (GIT) are disrupted triggering an imbalance in the gut microbiome and disruption in the microbiome–gut–brain axis (Carding et al. 2015; Noble et al. 2017). Conventionally, gut dysbiosis has been implicated in several chronic gastrointestinal tract related diseases and disorders, such as irritable bowel syndrome (IBS) (Menees and Chey 2018), colorectal cancer (Sobhani et al. 2013), celiac disease (Marasco et al. 2016), and also in metabolic disorders such as type 2 diabetes (T2D) and obesity (Belizário et al. 2018). However, gut microbiome dysbiosis has also been observed to impact the GBA, ultimately affecting the CNS and functions related to behaviour and cognition (Carding et al. 2015), clearly suggesting the microbial control of the GBA.

11.2 Microbial Control of the Gut–Brain Axis (GBA)

The gut–brain axis is inclusive of the central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), the gut microbiota, and the endocrine and immune systems (Carabotti et al. 2015). This bidirectional interaction also includes the modulation of gut physiology by the CNS and its influence on functions of the gut such as motility, nociception, and immune function (Fung et al. 2017). The vagus nerve connects the ENS to the CNS, thus providing a direct communication pathway between the gut microbiome and the CNS facilitating the modulation of the CNS by neurotransmitters or other metabolites produced by the bacteria of the gut (Forsythe et al. 2014). Neurotransmitters are endogenous chemical messengers which diffuse signals across a chemical synapse from one neuron to

another neuron, gland cell, or muscle cell (Lodish et al. 2000). The ability of specific bacterial species of the gut microbiota to produce and modulate neurotransmitters and related receptors has been demonstrated by a number of studies (Strandwitz 2018; Wu et al. 2020). In a study with normal mice, ingestion of *Lactobacillus rhamnosus* JB-1 induced region-dependent changes in the expression of gamma aminobutyric acid (*GABA*) receptor levels in the brain and reduced anxiety and depression related behaviour, with the vagus nerve identified as the major communication pathway between the gut and the brain (Bravo et al. 2011). Studies in gem free mice have shown increased activity related to transcriptional pathways in the amygdala (Stilling et al. 2015), increase in levels of noradrenaline and dopamine and 5-hydroxytryptamine (5-HT) in the striatum (Diaz Heijtz et al. 2011), and decrease in levels of 5-HT and 5-HT1A receptor expression in the hippocampus and amygdala (Neufeld et al. 2011; Diaz Heijtz et al. 2011). Studies have also thrown light on the ability of gut bacteria to produce several neuroactive compounds, for example, serotonin by *Candida, Streptococcus, Escherichia* and *Enterococcus* species, norepinephrine by *Escherichia*,
Saccharomyces, and *Bacillus* species, acetylcholine by *Lactobacillus* species, GABA by *Bacillus* and *Bifidobacterium*, and dopamine by *Bacillus* and *Serratia* species (Lyte 2011). The neurotransmitters that are unable to cross the blood–brain barrier exert their action by stimulating the vagus nerve, consequently affecting brain functions (Barrett et al. 2012).

One of the systems known for its close interaction with the gut microbiota is the hypothalamic–pituitary–adrenal (HPA) axis, the major neuroendocrine system of the body. The communication between the HPA axis and gut microbiota is closely associated with the immune system, gut hormones, as well as the autonomic nervous systems (Mayer 2000). In response to stress, paraventricular neurons of the hypothalamus release corticosterone-releasing factor (CRF), which then induces the anterior pituitary gland to release of adrenocorticotropic hormone (ACTH) (Foster et al. 2017). The release of ACTH will induce the release of catecholamines, glucocorticoids, or mineralocorticoids which can influence both behaviour and intestinal microenvironment (Farzi et al. 2018). Various studies have been published that have demonstrated the influence of stress on gut microbiome composition (Bailey and Coe 1999; Bailey et al. 2011). In addition, gut microbiota can modulate the expression of CRF in the hypothalamus (Crumeyrolle-Arias et al. 2014) and the expression of 2A subtype Of N-methyl-D-aspartic acid (NMDA) receptor, brain-derived neurotrophic factor (BDNF), and 5-HT1a receptors in the cortex and hippocampus (Ka et al. 2016), thus influencing the function of the HPA axis.

The host gut microbiome can modulate the maturation and function of microglia (Erny et al. 2015) and influence the activation of peripheral immune cells (Fung et al. 2017). Pathogen-associated molecular patterns (PAMPs), for example, lipopolysaccharides (LPS), can stimulate host immune cells to produce various peripheral various proinflammatory cytokines such as TNF-α, IL-1α, IL-1β, and IL-6 (Dantzer 2009). PAMPs and peripheral cytokines stimulate the macrophage like cells in the circumventricular organs (CVOs) and choroid plexus, to produce brain proinflammatory cytokines that diffuse by volume propagation into the brain

parenchyma (Sherry et al. 2010). The peripheral cytokines can also activate the vagal afferents providing a rapid signalling pathway. In both these events, the activity of brain proinflammatory cytokines can be mediated by either prostaglandins that diffuse to brain targets or by activation of neural pathways within the brain bringing about alteration in neurological functions (Dantzer et al. 2000; Dantzer 2009)

Microbial fermentation of complex polysaccharides/prebiotics in the intestine may increase the production of short-chain fatty acids (SCFAs), such as butyric, acetic, and propionic acid which are capable of crossing the blood–brain barrier (BBB) and able to elicit neurological response (Silva et al. 2020). SCFAs interact with their receptors on enteroendocrine cells and indirectly signal the brain via either the systemic circulation or through vagal pathways by stimulating the secretion of neurotransmitters such as GABA and 5-HT (Sherwin et al. 2018) and gastrointestinal tract (GIT) hormones such as glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) (Cherbut et al. 1998). SCFAs can cross the BBB and upregulate the expression of tight junction proteins, ultimately influencing integrity of the BBB (Silva et al. 2020). In the CNS, SCFAs contribute to the biosynthesis of serotonin (Reigstad et al. 2015), increase neurogenesis, (Kim et al. 2009) and impact neuroinflammation by influencing glial cell morphology and function and moderating the levels of neurotrophic factors (Savignac et al. 2013). Thus, interaction of SCFAs can indirectly or directly influence the pathophysiology of brain disorders as well as emotion and cognition.

11.3 Dysbiosis and Disorders Related to Gut–Brain Axis

Gut microbiota can affect neurological functions via many complex pathways evident by the fact that many neurological disorders are associated with dysbiosis in the gut. In addition, the rate of psychiatric disorders (especially depressive and anxiety disorders) has been found to be considerably high among patients with functional gastrointestinal disorders (Lydiard and Falsetti 1999). There a number of studies that support the hypothesis that gut dysbiosis can result in altered gut–brain axis resulting in neurobiological disorders (Griffiths and Mazmanian 2018), neurodevelopmental disorders (Stilling et al. 2015; Lacorte et al. 2019), and impaired cognitive function (Novotný et al. 2019). Increased gut permeability is also speculated to be strongly correlated with behavioural changes. In fact, many of the functional GI disorders such as IBS, functional dyspepsia are associated with increased gut permeability, chronic inflammation, and anxiety and depressive disorders (Barry and Dinan 2006; Jones et al. 2017). Further, a clinical study of patients with alcohol addiction reinforced the link between increased gut permeability and depression and anxiety (Leclercq et al. 2014). A few representative studies related to the involvement of gut dysbiosis in various neurological and psychiatric disorders are discussed below.

Alzheimer's disease (AD), a neurodegenerative disorder, is characterized by a progressive decline in behaviour, cognitive function, and social skills. AD is associated with the formation of amyloid beta (Aβ) plaques and neurofibrillary

tangles (DeTure and Dickson 2019). The bacteria of the GIT are source of a significant amount of amyloids. In the gut, the exposure to bacterial amyloid may result in the activation of immune cells which subsequently enhances formation of neuronal amyloid in the brain (Kowalski and Mulak 2019). The role of bacterial amyloid in triggering AD is evident from a number of studies. Rats exposed to *E. coli* that produced curli (bacterial amyloid) displayed increase in deposition of neuronal alpha-synuclein (α-syn) in both the brain and gut, and augmented astrogliosis and microgliosis compared to rats exposed to mutant bacteria lacking the ability to produce curli (Chen et al. 2016). Similarly, α-syn expressing *C. elegans* fed on curli-producing bacteria displayed greater α-syn aggregation (Chen et al. 2016). The prevalence of bacterial components such as *E. coli* pili protein (Zhan et al. 2016) or nucleic acids (Emery et al. 2017) is greater in the brain of AD patients. *H. pylori* infection is also linked with AD. It has been reported that AD patients with *H. pylori* infection have low Mini-Mental State Examination scores corresponding with serious cognitive dysfunction (Kountouras et al. 2009). Vogt et al. (2017) reported gut microbiota alterations in AD patients characterized by lower microbial diversity, decreased abundance of *Bifidobacterium and Firmicutes*, and increased abundance of *Bacteroidetes*.

Parkinson's disease (PD) is a neurodegenerative disorder characterized by neuroinflammation

and loss of midbrain dopaminergic neurons and manifested by motor symptoms such as rigidity, tremors, and bradykinesia (Poirier et al. 2016). Growing evidence suggests that motor impairments are usually preceded by nonmotor symptoms mainly constipation, depression, sleep behaviour disorder, and olfactory deficit, sometimes by up to a decade (Chaudhuri and Schapira 2009). A recent study reported significant decrease in the abundance of *Prevotellaceae* in PD patients and a positive association between the abundance of *Enterobacteriaceae* and the severity of instability of posture and gait difficulty, strongly implying the role of the bacteria of the gut in the PD phenotype (Scheperjans et al. 2015). Interestingly, abnormally aggregated Lewy bodies (α-synuclein) which are the pathohistological hallmark of PD are reported to be observed in the ENS before it appears in the CNS (Braak et al. 2006). In addition, experiments have demonstrated the spread of α-synuclein from the intestinal wall to the vagus nerve and hence the CNS (Goehring et al. 2014). Another study reported significant decrease in the concentration of SCFA in the faeces of PD patients compared to controls. This was accompanied by reduction in abundance of bacterial phylum *Bacteroidetes* and the bacterial family *Prevotellaceae* and increase in abundance of *Enterobacteriaceae* (Unger et al. 2016). These studies provide direct evidence of the spread of PD pathology from GIT to CNS via the gut–brain axis.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder which includes repetitive patterns of behaviour that influences how a person perceives and socializes with others, causing problems in communication and social interaction (Faras et al. 2010). ASD has been reported to be associated with GIT problems, such as overgrowth of intestinal pathogenic bacteria, abnormal gastrointestinal fistula, indigestion, and poor absorption in children (Fond et al. 2015). Alterations

in the composition of the gut microbiota and its metabolites have been demonstrated both in ASD children and animal models of ASD (De Angelis et al. 2015; Kushak et al. 2016). Fine gold and colleagues reported higher levels of *Desulfovibrio* species and *Bacteroides vulgatus* in faeces of severely autistic children compared to control (Finegold et al. 2010). *Bacteroidetes* produce propionic acid which may influence CNS and autism behaviour. Kang et al. (2013) reported lower levels of carbohydrate-degrading and/or metabolizing bacteria of the genera *Prevotella*, *Coprococcus*, and unclassified *Veillonellaceae* in autistic children. Gastrointestinal *Candida albicans*, a fungus which is known to release autistic behaviour inducing ammonia and other toxins, was reported to be two times more abundant in toddlers with ASD compared to normal individuals (Iovene et al. 2017).

Multiple sclerosis (MS) is a common neurological disease typified by an autoimmune inflammatory response in which immune cells affect brain and spinal cord cells resulting in demyelination and damage to the axon (Tremlett et al. 2016a). Studies have shown that MS patients have lower proportion of *Faecalibacterium* (Cantarel et al. 2015). This dysbiosis is significant because reduction in the population of *Faecalibacterium* spp. results in decrease in levels of its metabolite butyrate leading to decrease of Treg cells and proinflammatory cytokines (Sokol et al. 2008). In a study with 18 relapsing-remitting MS cases and 17 controls, it was noted that MS subjects had a significant augmentation in relative abundance of members of the *Desulfovibrionaceae* (*Bilophila*, *Desulfovibrio*, and *Christensenellaceae*) and reduction in *Lachnospiraceae* and *Ruminococcaceae*. In addition various other studies provide evidence on the prominence of the changes in composition of gut microbiota in MS (Tremlett et al. 2016a; Adamczyk-Sowa et al. 2017).

Major Depressive Disorder (MDD) also referred to as clinical depression is a psychological state characterized by persistent feeling of sadness and loss of interest, accompanied by several psychophysiological changes, such as loss of appetite, or sexual desire, disturbances in sleep pattern and constipation (Verduijn et al. 2015). Over the past decade, increasing number of studies have reported altered gut microbiota constitution in major depressive disorder (MDD) patients. Aizawa et al. (2016) reported reduction in *Bifidobacterium* and/or *Lactobacillus* counts in patients with MDD compared with normal individuals. Remarkably, attenuation of depression related behaviours could be achieved by intervention using probiotic *Bifidobacterium* (Desbonnet et al. 2008; Savignac et al. 2014) *and Lactobacillus* (Messaoudi et al. 2011; Bravo et al. 2011) *and prebiotic fructooligosaccharides and galactooligosaccharides* (Burokas et al. 2017). Furthermore, the counts of bacteria such as *Prevotella*, *Klebsiella*, *Streptococcus*, and *Clostridium* XI were found to be higher in MDD patients (Lin et al. 2016).

The gut microbiota has also emerged as a vital influencer of cognitive health (Desbonnet et al. 2008; Noble et al. 2017). Fröhlich et al. (2016) reported that recognition of novel objects was compromised in mice with antibiotic treatment induced dysbiosis. This cognitive deficit was correlated with alteration in the expression of cognition-relevant signalling molecules of the brain such as serotonin transporter, neuropeptide Y system, brain-derived neurotrophic factor, and N-methyl-D-aspartate receptor subunit. Additionally, Lee et al. (2019) reported that

suppression of gut dysbiosis by *Bifidobacterium longum* can alleviate cognitive decline in mouse model. Studies investigating the link between gut dysbiosis and neurological and psychiatric disorders are summarized in Table 11.1.

In addition to the studies mentioned above one can find myriad studies relating gut dysbiosis and neurological and psychiatric disorders (Douglas-Escobar et al. 2013; Rogers et al. 2016; Clapp et al. 2017). While the mechanistic details still remain to be determined, these recent advances suggest that modulating the composition of the microbiota appears to be a viable therapeutic option for modulating neurological and psychiatric disorders and may improve quality of life. This can be achieved in part by effective prebiotic intervention. The following section highlights different types of prebiotics that can be effectively used for addressing gut dysbiosis and consequently achieving healthy gut–brain axis.

11.4 The Concept of Prebiotics

Several therapeutic strategies have been employed to re-establish and/or to maintain the equilibrium in the microbial ecosystem of the intestine. These include the consumption of probiotics, prebiotics, and synbiotics (Gagliardi et al. 2018), phage therapy (Scarpellini et al. 2015), bacterial consortium transplantation (BCT), and faecal microbiota transplantation (FMT) (Li et al. 2015). In the recent years, use of prebiotics is becoming increasingly popular as a safe dietary approach for overcoming gut dysbiosis. Prebiotics and the metabolites formed by their fermentation in the gut play a vital role in management of gut dysbiosis and hence modulate the gut–brain axis (Franco-Robles et al. 2019).

The concept of prebiotics was introduced in 1995 by Glenn Gibson and Marcel who first defined prebiotics as 'nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thus improving host health' (Gibson and Roberfroid 1995). Accordingly to classify a compound as prebiotic it should be resistant to the acidic pH of stomach; should not be digested/hydrolysed by mammalian enzymes nor be absorbed in the gastrointestinal tract; should be fermented by intestinal microbiota and should selectively stimulate the growth and/or activity of the intestinal bacteria that confer health benefits on the host (Gibson et al. 2010). Most of the first prebiotics evaluated in humans and used commercially were shown to enrich *Lactobacillus* and/or *Bifidobacterium* specifically (Didari et al. 2014). Over the last two decades, prebiotics and the concept around it have constantly been debated and the definition of prebiotics has seen an evolution to include all perspectives. In December 2016, a panel of experts in nutrition, biochemistry, microbiology, and clinical research convened by International Scientific Association of Probiotics and Prebiotics (ISAPP) updated the definition of a prebiotic to 'a substrate that is selectively utilized by host microorganisms conferring a health benefit' thus expanding the beneficiary role of prebiotics to body sites other than the GIT, and provide inclusion of diverse classes of food and non-food categories. It recognizes the health benefits derived from prebiotic stimulation of not only *Lactobacillus and*

Table 11.1 Studies investigating the link between gut dysbiosis and neurological and psychiatric disorders

Neurological disease/ disorder	Study design and sample	Gut dysbiosis-Altered gut microbiota and / or metabolites (As compared to control)	Reference
Alzheimer's disease	*AD patients with dementia and non-demented control participants.* Sample: Faecal sample	*Bifidobacterium and Firmicutes* ↓ *Bacteroidetes* ↑	Vogt et al. (2017)
Parkinson's disease	*PD patients and age-matched control* Sample: Faecal sample	*Enterobacteriaceae* ↑ Bacteroidetes ↓ *Prevotellaceae* ↓ SCFA↓	Unger et al. (2016)
Parkinson's disease	*PD patients and healthy control* Sample: Mucosa and Faecal sample	Faecal Sample Putative 'anti-inflammatory' butyrate producing bacteria from the genera *Blautia*, *Coprococcus*, and *Roseburia* ↓ Mucosa Sample *Faecalibacterium* ↓ Putative, 'proinflammatory' proteobacteria of the genus *Ralstonia* ↑	Keshavarzian et al. (2015)
Autism	Neurotypical and autistic children Sample: Faecal sample	*Prevotella, Coprococcus,* and unclassified *Veillonellaceae* ↓	Kang et al. (2013)
Autism	Autistic subjects and non-autistic control (sibling and non-sibling) Sample: Faecal sample	Bacteroidetes ↑ *Desulfovibrio* species and *Bacteroides vulgatus*↑ Firmicutes ↓	Finegold et al. (2010)
Major depressive disorder	MDD patients and Control Sample: Faecal sample	*Bifidobacterium* and *Lactobacillus* ↓	Aizawa et al. (2016)
Major depressive disorder	MDD patients and Control Sample: Faecal sample	*Bacteroidetes, Proteobacteria,* and *Actinobacteria* ↑ *Firmicutes* ↓	Jiang et al. (2015)
Major depressive disorder	MDD patients and Control Sample: Faecal sample	*Prevotella*, *Klebsiella*, *Streptococcus*, and *Clostridium* XI ↑	Lin et al. (2016)
Multiple sclerosis	MS patients and Control Sample: Faecal sample	*Ruminococcus* ↑ *Faecalibacterium* and *Bacteroidaceae* ↓	Cantarel et al. (2015)
Multiple sclerosis	MS patients and Control Sample: Faecal sample	*Desulfovibrionaceae (Bilophila, Desulfovibrio, and Christensenellaceae)* ↑ *Lachnospiraceae and Ruminococcaceae* ↓	Tremlett et al. (2016b)

Abbreviations: *AD* Alzheimer's Disease, *PD* Parkinson's Disease, *MDD* Major Depressive Disorder; *MS* Multiple Sclerosis, *SCFA* Short Chain Fatty acids

Bifidobacterium but also of other beneficial taxa which include (but not limited to) *Eubacterium*, *Roseburia*, or *Faecalibacterium* spp. (Gibson et al. 2017). Substrates that influence gut microbiota composition through mechanisms different from selective utilization by host microorganisms are excluded from the prebiotic bracket, for example, antibiotics, minerals, vitamins, and bacteriophages (Gibson et al. 2017). Another term of interest in the context of prebiotics is *Dietary fibre*. Codex Alimentarius Commission in 2009, defined Dietary fibre as 'carbohydrate polymers with 10 or more monomeric units, which are neither digested nor absorbed in the human small intestine'. They include naturally occurring edible carbohydrate polymers in food; edible carbohydrate polymers extracted (physically, enzymatically, or chemically) from food raw material, and edible synthetic carbohydrate polymers with beneficial physiological effect (Codex Alimentarius Committee 2010). The flexibility in the definition of dietary fibre is evident by the fact that many countries include non-digestible carbohydrates with greater than three monomeric units under the bracket of dietary fibre (Jones 2014).

To date, prebiotic properties have been ascribed primarily to carbohydrates, especially non-digestible oligosaccharides (NDO) and a few complex carbohydrates; however some compounds that are not carbohydrates are also recommended to be classified as prebiotics, for example, cocoa-derived flavanols (Tzounis et al. 2011); whey derived protein, glycomacropeptide (GMP) (Sawin et al. 2015), and polyunsaturated fatty acid (PUFA) (Gibson et al. 2017). Since majority of the substrates studied for their prebiotic potency are dietary carbohydrates, in the present chapter we will focus only on the impact of dietary carbohydrates as prebiotics.

11.4.1 Prebiotic Dietary Carbohydrates

Prebiotic dietary carbohydrates are **carbohydrates** present in food that are speculated to be able to

11.4.1.1 Oligosaccharides as Prebiotics

Over the past few decades, different types of oligosaccharides have been reported to possess prebiotic potency, among them inulin-type fructans [inulin, oligofructose, and fructooligosaccharides (FOS)], lactulose, and galactooligosaccharides (GOS) are the only dietary carbohydrates that are reported to fulfil all the criteria for classification as prebiotics (Davani-Davari et al. 2019). An interesting *class* of oligosaccharides included in the prebiotic category are the *human milk oligosaccharides* (*HMOs*). HMOs play a very important and crucial role in shaping infant gut microbiome (Pannaraj et al. 2017). Xylooligosaccharides (XOS), isomalto-oligosaccharides (IMO), raffinose family oligosaccharides (RFO), lactitol and a range of other oligosaccharides are included under emerging prebiotics.

Inulin-Type Fructans

Inulin-type fructans (ITF) are polymers of fructose with β-(2←1) fructosyl-fructose linkages with degree of polymerization (DP) varying from 1–60. Both $F_{py}F_n$

[fructopyranosyl-(fructofuranosyl)$_n$-fructose] and $G_{py}F_n$ [glucopyranosyl-(fructofuransoyl)$_n$-fructose] are included under this nomenclature. ITF include native inulin (DP, 2–60), inulin HP (DP, 10–60) oligofructose (OF), and fructo-oligosaccharides (FOS) (DP, 2–8) (Roberfroid 2007). ITF can be extracted from plants (native chicory inulin), produced from enzymatic hydrolysis of inulin (e.g. oligofructose), or enzymatically synthesized from sucrose (e.g. FOS) (Roberfroid 2007). In addition to these, two ITF products; (i) 'Synergy' containing long-chain inulin and short-chain oligofructose and (ii) 'scFOS' containing a mixture of three oligosaccharides of DP3–5 are also available commercially (Hidaka et al. 1986). Owing to β-configuration of the anomeric C_2 in its fructose monomers, ITF can resist digestion/hydrolysis by mammalian digestive enzymes which are known to be specific for α-glycosidic bonds, making ITF excellent prebiotic substrates (Roberfroid 2007).

Galactooligosaccharides (GOS)

Galactooligosaccharides (GOS), also known as oligolactose, or oligogalactosyllactose, are oligosaccharides of β-D-galactopyranosyl units (2–8) with a terminal (reducing end) D-glucose. Conventionally, GOS are prepared from lactose by transglycosylation reaction using the enzyme β-galactosidase, which adds D-galactopyranosyl monomers to the nonreducing end of lactose, forming a family of oligosaccharides of varying chain length comprising a mixture of (1 → 4) and (1 → 6) linkages (BeMiller 2019). GOS produced from transglycosylation reaction are termed as trans-galactooligosaccharides (TOS). β-galactosidases are derived from various fungal and bacterial sources such as *Aspergillus* (Vera et al. 2012), *Bifidobacteria* (Rabiu et al. 2001), and *Lactobacilli* (Iqbal et al. 2011). The yield, degree of polymerization, and glycosidic linkages differ based on the source from which β-galactosidase is derived (Zárate and López-Leiva 1990). Recently, a unique second-generation prebiotic GOS was produced using galactosidase enzymes obtained from *Bifidobacterium bifidum* NCIMB 41171 (Tzortzis et al. 2005). This GOS referred to as B-GOS (Bimuno® 52 % GOS content; Clasado Biosciences Ltd) contains GOS in β-and α-anomeric configuration (Tzortzis 2010).

Human Milk Oligosaccharides (HMOs)

Human milk oligosaccharides are a complex group of glycans found in human milk at a concentration of 20–25 g/L in colostrum and 10–15 g/L in mature milk (Coppa et al. 1999). More than 200 different oligosaccharides have been reported in human milk with their carbohydrate chain containing lactose (Galβ1-4Glc) at the reducing end, which may be extended by the addition of β1-3- or β1-6-linked lacto-*N*-biose (type 1 chain) or *N*-acetyllactosamine (type 2 chain) (Bode 2012). The principle monosaccharides of HMOs are D-galactose, D-glucose, L-Fucose, N-acetylglucosamine, and sialic acid. Based on their structure and substitution, HMOs are classified as sialylated acidic HMOs, fucosylated neutral HMOs, and non-fucosylated neutral HMO (Vandenplas et al. 2018). Among the huge repertoire of soluble glycan structures of HMO, 2′-fucosyllactose (2′-FL) is reported to be the most abundant (Erney et al. 2000).

11.4.1.2 Complex Polysaccharides

Complex polysaccharides which are abundant in plant-based diet reach the intestine unaltered. Many complex polysaccharides are soluble and are easily fermented by the intestinal microbiota and thus serve as prebiotics (Flint et al. 2012). Fermentable complex polysaccharides which are known for their prebiotic potency include arabinoxylans, beta-glucans, resistant starch, glucomannans, and fucoidan.

i. Arabinoxylans are non-digestible polysaccharides mainly found in the bran tissues of most cereals (Hopkins et al. 2003). Arabinoxylans consist of unsubstituted β-(1-4) linked xylose backbone with α-(1-3) arabinofuranosyl or α-(1-2) L-arabinofuranosyl or a double α-(1-2) and α-(1-3) arabinofuranosyl linked to the xylose backbone with or without uronic acid (galacturonic acid, glucuronic acid, and mannuronic acid) and phenolic acid (mainly ferulic acid and p-coumaric acid) substitution (Bajpai 2014).
ii. Resistant starch is a portion of dietary starch that cannot be digested by amylases of the GIT and reaches the colon to be fermented by microbiota (Englyst and Cummings 1985). Currently, 5 types of resistant starch have been identified: RSI-Physically inaccessible starch, RSII-Granular starch with the B- or C-polymorph, RSIII-Retrograded starch, RSIV-Chemically modified starches, and RSV-Amylose-lipid complex (Birt et al. 2013).
iii. Beta-glucans are non-starch polysaccharides consisting of repeating glucose residues forming either linear chains or branched structures (Lam and Chi-Keung Cheung 2013). The primary structure, branching pattern and degree of branching, molecular weight (MW), and solubility are involved in the biological activity exhibited by beta-glucan and vary according to the source (Zeković et al. 2005).
iv. Glucomannans are neutral polysaccharides produced by many plants, especially the *Amorphophallus* family (e.g. Konjac). These polysaccharides predominately comprise mannose units with glucose as the second most abundant sugar, and may contain some acetylated residues and galactose side chains (Al-Ghazzewi et al. 2007). Konjac glucomannans typically have high molecular weight ($>1 \times 10^6$ Da), and are commonly used in the food industry as a gelling and thickening agent owing to their exceptionally high swelling characteristics when hydrated (Akesowan 2002).
v. Fucoidan is a fucose-enriched, sulphated polysaccharide that is primarily extracted from brown algae. Along with L-fucose and sulphate groups, fucoidan consists of one or more units of mannose, galactose, xylose, glucose, arabinose, rhamnose, glucuronic acid, and acetyl groups (Luthuli et al. 2019).

11.5 Prebiotics in Management of Dysbiosis

Based on the emerging appreciation of the link between the brain and the gut microbiota, it is evident that management of gut dysbiosis has direct beneficial impact on the gut–brain axis, hence restoration of dysregulated microbiota has

therapeutic consequences. This can be achieved by boosting bacterial growth using *prebiotics. Additionally, the metabolites produced by the intestinal bacteria in the process of prebiotic fermentation have a positive impact on host physiology* (Tsai et al. 2019). *Research over the years has identified specific strains of bacteria whose abundance in the gut would bring about a positive impact on the microbiome quality and on health condition and is termed as beneficial bacteria. Some examples of beneficial bacteria include Lactobacillus reuteri* (Gao et al. 2015)*, Lactobacillus rhamnosus*JB-1 (Bravo et al. 2011), *Lactobacillus acidophilus, Bifidobacterium animalis* subsp. *lactis, Prevotella* (Ou et al. 2013)*, Faecalibacterium prausnitzii* (Scott et al. 2015)*, Bacillus subtilis* HU58 (Tam et al. 2006), etc. In fact, a host of bacterial species belonging to the lactobacilli and bifidobacterial genera are considered beneficial/ probiotic (Fijan 2014). *Currently the dysbiosis management strategies are focussed towards increasing the population of these beneficial bacteria.*

Different approaches are employed to study the ability of dietary carbohydrates to selectively propagate the growth of beneficial bacteria and induce the production of specific SCFAs, and thus modulate the gut microbiome. The simplest and the most widely applied approach is the in vitro studies. There are numerous in vitro studies on the ability of dietary carbohydrates to enhance the growth of specific strains of bacteria (Su et al. 2007; Ward et al. 2007; Pastell et al. 2009; Kunová et al. 2012; Ramnani et al. 2012; Sims et al. 2014; Liu et al. 2016). *Additionally*, in vitro fermenters have been employed in an attempt to mimic intestinal conditions using colon simulators (Gibson and Wang 1994; Macfarlane et al. 1998; Mäkeläinen et al. 2010). *In addition to evaluating their prebiotic potency, researchers have also analysed the ability of dietary carbohydrates to* inhibit the growth of selected human intestinal pathogens (Fooks and Gibson 2002). *In vitro studies are helpful in proposing the prebiotic potency of dietary fibre; however, these studies need to be validated by in vivo experiments.* In vivo studies generally use animal models such as rats or mice or human clinical trials, to determine the effect of prebiotic supplementation on host faecal microflora. Rats or mice provide limited representation of the situation in the human colon, hence the results may not indicate true effect (Shanks et al. 2009). Therefore, the most efficient approach is the human volunteer Randomized Controlled Trial (RCT) study. Human trials are usually done by faecal sampling after diet supplementation with dietary carbohydrates for a fixed experimental period. Various in vivo studies with human volunteers have reported the ability of dietary carbohydrates to selectively stimulate the growth of bifidobacterial, lactobacilli, and other genera, inhibit the growth of pathogenic bacteria, and increase the concentration of specific SCFA (Table 11.2). However, the major drawback of human trials is that analysis of the different regions of the gut is not possible and only faecal matter is readily available.

Table 11.2 Examples of *in vivo* studies (Human volunteers) designed to determine the ability of prebiotic dietary fibre to modulate gut microbiome and impact gut ecology

Prebiotic	Volunteers	Study Design	Dosage	Changes in gut-microbiome ecology	Reference
Bi2muno Galactooligosaccharide (B-GOS)	45 overweight adults with risk factors for metabolic syndrome.	12 weeks, randomized, double-blind, cross-over (4-week wash-out period), placebo-controlled design.	5.5 /day	*Bifidobacterium*↑ *Bacteroides* spp. ↓ *C. histolyticum* ↓ *Desulfovibrio* spp↓	Vulevic et al. (2013)
Trans-galactooligosaccharide (T-GOS)	44 patients with Rome II positive IBS. Age: 18 and 80 years	12-week, single centre, parallel, patient blinded, randomized cross over controlled design.	3.5 or 7 g/day	At 3 g and 7 g *Bifidobacterium* spp. ↑ At 7 g *C. perfringens* subgroup *histolyticum* ↓ *Bacteroides/Prevotella* spp. ↓	Silk et al. (2009)
Inulin type fructans (Synergy 1)	30 overweight females Age: 18–65 years BMI: >30 kg/m^2	12 weeks, randomized, double-blind, parallel, placebo-controlled design.	16 g/day	*Bifidobacterium longum* ↑ *Bifidobacterium pseudocatenulatum* ↑ *Bifidobacterium adolescentis*↑ Total SCFA↓ Acetate↓ Propionate↓	Salazar et al. (2015)
Agave Inulin	29 Healthy adults (15F, 14M) Age: 20–40 years BMI: 18.5–29.5 kg/m^2	3-week, randomized, double-blind, placebo-controlled, cross-over design.	5.0 or 7.5 g/day	*Bifidobacterium* ↑ *Ruminococcus*↓ *Lachnobacterium*↓ *Desulfovibrio*↓	Holscher et al. (2015)
Inulin-oligofructose	12 healthy volunteers	21-days, controlled, randomized, cross-over design.	10 g/day	*Faecalibacterium prausnitzii* ↑ *Bifidobacterium adolescentis* ↑ *Bifidobacterium bifidum* ↑	Ramirez-Farias et al. (2009)

(continued)

Table 11.2 (continued)

Prebiotic	Volunteers	Study Design	Dosage	Changes in gut-microbiome ecology	Reference
				Bifidobacterium longum ↑ SCFA-NC Lactate-NC pH-NC	
FOS	10 patients with active ileocolonic Crohn's disease Age: 18–84 years	3-week dietary intervention.	15 g/day	*Bifidobacterium* ↑	Lindsay et al. (2006)
XOS and Inulin + XOS (INU-XOS)	60 healthy adults (34F, 36M) Age: 18–24 years BMI: 18·5–27 kg/m^2	4-week, randomized, parallel, placebo-controlled, double-blind design.	5 g XOS (XOS group) 3 g inulin + 1 g XOS (INU–XOS group).	XOS *Bifidobacterium* ↑ Butyrate ↑ Acetate↓ p-cresol↓ pH↓ INU-XOS *Bifidobacterium* ↑ Total SCFA↑ Propionate↑	Lecerf et al. (2012)
Resistant starch	14 obese males Age: 27–73 years BMI: 27.9–51.3 kg/m^2	3-week, randomized cross-over design.	22–29 g/d	*Oscillospira guillermondii* ↑ *Ruminococcus bromii* ↑ *Sporobacter termitidis*↑ *Clostridium leptum* ↑ *Clostridium cellulosi* ↑ *Papillibactercinnamivorans* ↓ *Alistipes* spp. ↓ Acetate ↓	Salonen et al. (2014)

				Propionate ↓ Butyrate↓	
Lactulose	16 healthy volunteers (5M, 11F) Age: 19–42 years	6-week, controlled, randomized, double-blind, parallel group design.	5 g/day	*Bifidobacterium* ↑ Total anaerobes-NC *Lactobacillus* -NC pH-NC	Bouhnik et al. (2004)
Arabinoxylan-oligosaccharides (AXOS)	63 healthy subjects (30F, 33M) Mean Age: 42 ± 17 years Mean BMI: 23.3 ± 3.2 kg/m^2	1-week run-in period, followed by three 3-week treatment periods with 2-week wash-out periods. Double-blind, randomized, placebo-controlled, cross-over deign.	3 or 10 g/day	*Bifidobacterium*↑ Acetate↑ Propionate↑ Butyrate↑ pH↓	François et al. (2012)

Abbreviations: M Male; *F* Female; *NC* No change, *BMI* Body Mass Index

11.6 Influence of Prebiotics on Gut–Brain Axis

The selective stimulation of beneficial bacteria by prebiotics not only helps in the management of dysbiosis but may also has a positive impact on the gut–brain axis. Though the mechanism of action of prebiotics on the gut–brain axis is still not conclusively determined, SCFAs are speculated to play a vital role. SCFAs are organic acids (saturated fatty acids) with a chain length ranging from one to six carbon atoms (Miller and Wolin 1996). The principle SCFAs released by the microbial fermentation of prebiotic substrates include butyrate, acetate, and propionate with the amalgamated concentration greater than 100 mM in the lumen of the intestine (Boets et al. 2017). Other SCFAs such as formate, caproate, and valerate are produced in lesser amounts (Macfarlane and Macfarlane 2003). SCFAs improve the gut health by exerting a number of local effects which include maintaining intestinal barrier integrity (Peng et al. 2009), provide protection from intestinal inflammation, affect mucous production in the gastrointestinal tract (Barcelo et al. 2000), influence gastrointestinal motility (Cherbut et al. 1998), and reduce the risk of colorectal cancer (Encarnação et al. 2015). In addition to the local effects, SCFAs are speculated to play a vital role in the crosstalk along the microbiome gut–brain axis owing to their effects directly on the CNS or indirectly via the immune and endocrine signalling pathways (Stilling et al. 2016; Dalile et al. 2019).

Studies conducted in rodent models and a few human trials have contributed immensely towards our understanding of the effect of prebiotics on neurobiological processes and consequently on the affective and cognitive functions. Sprague–Dawley rats administered with FOS, GOS, or water, over 5 weeks, showed increased expression of hippocampal brain-derived neurotrophic factor (BDNF) and NR1 subunit of *N*-methyl-D-aspartate receptor (NMDAR), with B-GOS additionally enhancing hippocampal NR2A subunits, and frontal cortex NR1 and D-serine (Savignac et al. 2013). The authors noted that GOS displayed superior neurostimulatory activity in comparison to FOS owing to the greater bifidogenic capacity of the former. The effect of supplementation of Bimuno formulation of galactooligosaccharide (B-GOS) has been studied in neonatal male and female Sprague–Dawley rat pups (Williams et al. 2016). Animals fed with B-GOS showed increased expression of hippocampal NMDAR subunit GluN2A, synaptophysin, BDNF, but not MAP2, suggesting that in neonates B-GOS feeding modifies neurotransmission rather than synaptic architecture. Based on the suggestion that BDNF may confer anxiolytic state, and NMDAR subunits may regulate cognitive functions it proposed that prebiotics can alter mood and cognitive abilities, via the modulation of microbiota (Savignac et al. 2013; Williams et al. 2016).

Salivary cortisol awakening response (CAR) and a validated test battery of emotional processing were used to assess neuroendocrine and affective effects (brain functions concerned with emotions) of prebiotics in healthy male and female participants ($n = 45$) who consumed either FOS, B-GOS, or a placebo (Schmidt et al. 2015). Amplified waking cortisol is a biomarker of psychological stress and emotional disturbances (Mannie et al. 2007; Shibuya et al. 2014). Results showed that the intake of B-GOS was linked with reduced waking salivary cortisol reactivity

and altered attentional bias in comparison with intake of FOS and placebo. Furthermore, B-GOS intake showed attenuated attentional vigilance to negative versus positive information in a dot-probe task in participants, suggestive of anxiolytic and antidepressive role of B-GOS. These studies strongly support the key role of gut microbiota modulating prebiotics in the regulation of affective function. Dietary intervention with scFOS (5 g/day) vs placebo for 4 weeks to treat IBS in patients is reported to increase faecal *Bifidobacterium* count and reduce anxiety scores (Azpiroz et al. 2017). Silk et al. (2009) evaluated the ability of a novel prebiotic trans-galactooligosaccharide (T-GOS, at doses 3.5 and 7.5 g/day) in managing colonic microbiota, improving IBS symptoms including managing anxiety and depression in patients suffering from IBS. Results indicated that T-GOS significantly improved anxiety/depression and subjective global assessment (SBA) scores. T-GOS treatment, at doses 3.5 and 7 g/day, resulted in significant increase in relative population of *Bifidobacterium* spp. The higher dose (7 g/day) of T-GOS resulted in lower proportion of *Bacteroides-Prevotella* spp. and *Clostridium perfringens* subgroup histolyticum, whereas lower T-GOS dose (3.5 g/day) resulted in higher proportion of *Eubacterium rectale*/*Clostridium coccoides* spp. Gronier et al. (2018) reported that rats ingesting B-GOS showed increase in the plasma acetate, and acetyl Co-A carboxylase mRNA, and cortical GluN2B subunits levels. Additionally, increase in neuronal responses to iontophoretically applied N-methyl-d-aspartate (NMDA) and improvement in intra-dimensional to an extradimensional set shifting in B-GOS fed rats were observed, thereby indicating heightened cognitive flexibility. Overall, the data demonstrated the association between pro-cognitive effect of B-GOS intake with an escalation in cortical NMDAR function, however the role of circulating acetate produced the B-GOS metabolism by the gut bacteria was not addressed. In another study, co-administration of B-GOS (0.5 g/kg/day) with olanzapine (antipsychotic drug) in adult female Sprague–Dawley rats significantly attenuated olanzapine-induced weight gain and had a positive effect on cognitive function (Kao et al. 2018). It was shown that in humans, FOS may modulate appetite by regulation of hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (Cani et al. 2009). Studies suggest that fructooligosaccharides from *Morinda officinalis* (OMO) exert effectual memory improvements in Alzheimer disease (AD)-like animals, and are effective in alleviating AD by affecting the gut–brain axis (Chen et al. 2013; Chen et al. 2017)

HMOs are reported to be crucial nutrients for neurological development in infants and essential for optimal *development* of cognitive abilities (Jacobi et al. 2016). A study in male rodents (both C57BL/6 mice and Sprague–Dawley rats) showed heightened associative learning and working memory associated with HMO glycan 2′-FL. Chronic administration of 2′-FL augmented the expression of phosphorylated calcium/calmodulin-dependent kinase II (pCaMKII), postsynaptic density protein 95 (PSD-95), and brain-derived neurotrophic factor (BDNF) in cortical and subcortical structures. These molecules are reported to be important in the storage of newly acquired memories, suggesting that dietary 2′-FL can affect cognitive domains and improve learning and memory in rodents (Vázquez et al. 2015). Another study revealed that oral supplementation of 2′-FL during lactation improved cognitive

abilities, both in childhood and adulthood (Oliveros et al. 2016). Two possible and nonexclusive mechanisms of action have been proposed to explain the neurobeneficial effects of HMO, a central mechanism according to which 2′-FL reaches the brain via systemic circulation (Goehring et al. 2014) and a local mechanism involving stimulation of the vagus nerve by 2′-FL (Murrey and Hsieh-Wilson 2008). All in all, whether the mode of action is via direct stimulation of the nervous system or indirectly via the microbiota, the molecular integrity of 2′FL is critical for induction of its effects.

Complex polysaccharides and polysaccharide-rich extracts modulate cognition, behaviour, and provide neuroprotective effects. Dietary intervention (14 days) with breakfast high in wheat bran fibre (3.5 g of wheat bran) in healthy, habitual low-fibre consumers significantly improved subjective perception of bowel function, digestive feelings, and general wellbeing (Lawton et al. 2013). Ambrotose Complex (a proprietary mixture of NSP) was observed to induce significant improvement in recognition and working memory performance, in healthy middle-aged adults (Best et al. 2010; Best et al. 2015). Similarly another study demonstrated that intervention with complex carbohydrates (6.5 g of fibre) is favourable in comparison to a simple carbohydrate breakfast, because of the higher degree of satiety and lower perception of fatigue associated with complex carbohydrate consumption (Pasman et al. 2003). Pectic polysaccharides have been reported to have anti-fatigue activity and improve the antioxidant status in the hippocampus of treated animals (Klosterhoff et al. 2018). Pectic polysaccharide consumption is also associated with improved intestinal barrier function resulting in prevention of lipopolysaccharide (LPS) entry into the circulation and reduction of influence of systemic inflammation on the brain. Supplementation with a Beta 1,3/1,6 glucan (250 mg, commercially available as Wellmune WGP®) for 4 weeks improved overall health, increased vigour, and reduced fatigue, tension, anger, and confusion, compared to 250 mg of rice flour placebo (Talbott and Talbott 2009).

Oral administration of isolichenan (*Cetraria islandica* derived alpha-glucan) to ethanol-fed mice reversed the ethanol-induced impairment (Smriga et al. 1999). Oral or intravenous injection of a new (1–3) (1–4) (3:2) α-glucan, isolated from the lichen *Flavoparmelia caperata*, resulted in potent, dose-dependent enhancement in tetanically evoked synaptic short-term potentiation (STP) in the hippocampus of rats (Smriga et al. 1996). Sherry et al. (2010) noted a basal up-regulation of IL-4 mRNA accompanied by doubling of endotoxin-induced IL-1RA expression in the brain of mice fed soluble fibre (pectin rich diet) in comparison with the mice fed insoluble fibre, indicating that the impact of soluble fibre is not limited to the gut and peripheral immune system but goes beyond and affects the neuroimmune system. In a neurotoxin (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)) induced animal model of Parkinson, fucoidan derived from the brown alga *Laminaria japonica* resulted in evident increase in tyrosine hydroxylase expression, increased levels of striatal dopamine and its metabolites, reduced behavioural deficits, and lowered cell death. In the same study, extended to *in vitro* model of PD, fucoidan shielded mouse dopaminergic MN9D cells from MPTP toxicity (Luo et al. 2009). In another study, intraperitoneal administration of Bladderwrack fucoidan reduced the

extent of hypoxia-ischemia induced neural damage in the cortex, hippocampus, and striatum of rat (Uhm et al. 2004). Arabinoxylan from *Triticum aestivum* (wheat) and beta-glucan from barely have been reported to have ameliorating effect against vascular dementia (Han et al. 2010). A uncharacterized polysaccharide fraction of *Panax ginseng* has been reported to promote learning and memory (Lyubimov et al. 1997). The impact of consumption of prebiotics on neurological disorders, cognition, and behaviour is summarized in Table 11.3.

11.7 Conclusion

The relationship demonstrated between the gut microbiome and the brain and the ability of prebiotics to modulate gut microbiome and thus impact gut–brain axis has garnered interest of researchers working towards developing diet-based therapies to manage neurological and psychiatric disorders. Although research in this direction has been initiated, there is limited understanding on the detailed mechanism of action of prebiotics. Developing therapeutic formulations using prebiotics requires deeper research into investigating the right dose, appropriate inclusion of probiotics, duration of treatment, and knowledge of associated side effects. It is also worthwhile to note that many dietary carbohydrates not bracketed under prebiotics have an impact on the CNS via routes that do not involve modulation of gut microbiome. Further, the involvement of food and pharmaceutical companies is required in terms of investment for large scale human trials. Prebiotic containing diet-based therapy in managing neurological and psychiatric disorders has a long road ahead.

Table 11.3 Studies investigating the impact of prebiotics on neurological disorders, cognition, and behaviour

Prebiotic	Study Model	Main finding	Inference	Reference
Fructooligosaccharide (FOS) and Galactooligosaccharide (GOS)	Adult male Sprague–Dawley rats	FOS and GOS increased hippocampal BDNF, NR1 subunit and *N* methyl-D-aspartate receptor (NMDAR) subunits expression Increased BDNF mRNA expression in dentate gyrus, GOS increased hippocampal NR2A subunits, and frontal cortex NR1 and D-serine and elevated plasma D-alanine and peptide YY (PYY).	FOS and GOS *could potentially* be used to treat *neuropsychiatric disorders*	Savignac et al. (2013)
Fructooligosaccharides from *Morinda officinalis* (OMO)	Adult male Sprague–Dawley AD-like symptoms rats.	OMO administration can ameliorate learning and memory disabilities in AD-like animals significantly.	FOS may have therapeutic effect in Alzheimer's disease	Chen et al. (2017)
Bimunogalactooligosaccharide (B-GOS) or Fructooligosaccharides (FOS)	Human: Healthy volunteers	B-GOS intake was associated with decreased waking salivary cortisol reactivity and altered attentional bias compared to FOS and placebo. Participants showed reduced attentional vigilance to negative versus positive information.	Anxiolytic and antidepressive role of B-GOS	Schmidt et al. (2015)
Short-chain fructooligosaccharides (scFOS)	Human: IBS patients	scFOS significantly reduced anxiety scores and increased faecal *Bifidobacteria*.	Anxiolytic effect of short-chain fructooligosaccharides (scFOS)	Azpiroz et al. (2017)
Bimuno™ galacto-oligosaccharide (B-GOS®)	Adult male Sprague–Dawley rats	B-GOS® administration augmented cortical neuronal responses to NMDA iontophoresis, partially hindered the reduction of NMDA responses HA-966 (glycine site antagonist) and resulted in	Pro-cognitive effect of B-GOS®	(Gronier et al. 2018)

		improvement in intra-dimensional to an extradimensional set shifting.		
Human milk oligosaccharides (HMO)-2′-fucosyllactose (2′-FL)	C57BL/6 mice and Sprague–Dawley rats	2′-FL enhanced associative learning and working memory and increased the expression of phosphorylated calcium/calmodulin-dependent kinase II (pCaMKII), postsynaptic density protein 95 (PSD-95), and brain-derived neurotrophic factor (BDNF) in cortical and subcortical structures-molecules reported to be important in the storage of newly acquired memories.	Positive impact of HMO-2′-FL on cognition.	Vázquez et al. (2015)
Beta 1,3/1,6 glucan (commercial name Wellmune WGP®)	Human trial: marathon runners	Beta-Glucan treated group reported significantly fewer upper-respiratory tract symptoms (URTI), decreased confusion, fatigue, anger, and tension, increased vigour, and better overall health.	Beta-glucan improves overall health and mood	Talbott and Talbott (2009)
Proprietary mixture of non-starch polysaccharides (NSPs) (Ambrotose® complex)	Human trial: middle-aged adults	Significant improvement in recognition and working memory performance was observed in the group that consumed NSP.	NSP may enhance memory performance	Best et al. (2015)
Oligofructose-enriched inulin	Human trial: Healthy adults	Inulin consumption was associated with greater accuracy on a recognition memory task, and improved immediate and delayed recall performance.	Positive effect of inulin on mood and memory	Smith et al. (2015)
Pectin	C56BL/6J mice injected i.p. with LPS	Pectin diet resulted in quicker recovery from LPS induced social withdrawal compared with cellulose diet.	Protective effect of pectin against endotoxin-induced sickness behaviour	Sherry et al. (2010)

(continued)

Table 11.3 (continued)

Prebiotic	Study Model	Main finding	Inference	Reference
Fucoidan	Neurotoxin induced animal model (C57/BL mice) of Parkinson	Fucoidan led to evident increase in tyrosine hydroxylase expression, increased levels of striatal dopamine and its metabolites, reduced behavioural deficits, and lowered cell death.	Protective effect of fucoidan against neurotoxin-induced neurodegeneration.	Luo et al. (2009)

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