REVIEW OF LITERATURE

CHAPTER 2

REVIEW OF LITERATURE

Functional constipation is one of the most common gastrointestinal disorders. Functional foods including prebiotics and probiotics, which are renowned for their potentially beneficial therapeutic effects in a variety of medical situations including gastrointestinal disorders. Galactooligosaccharide (GOS), one of the prebiotic, has gained attention for its tremendous potential in terms of enhancing bacterial bionomics, which may have a direct role in lowering the burden of gastrointestinal diseases.

In view of this, the present study was designed under the title, "**Presence of Functional Constipation in the Teaching staff of The M. S. University of Baroda and Impact Evaluation of Supplementation of Galactooligosaccharide (GOS) added Gummies on their Gut Health and Constipation Profile - A Randomised Double Blind Placebo Control Trial**". This chapter assembles the available review of literature for the study in to following sections.

Constipation:

The sure sign that your guts are giving you THE SILENT TREATMENT

2.1 Global and National prevalence of Digestive Diseases

The absence of disease or infirmity is not the only factor in determining one's level of health, according to the World Health Organization (WHO). Mortality and morbidity (the prevalent illness), collectively called as the "burden of disease," should both be taken into consideration for a comprehensive understanding of the health outcome of any society. The term "Disability Adjusted Life Years" (DALYs), which refers to years spent with a health burden, is used to quantify this. The concept of a DALY is the loss of one year of healthy life due to illness or incapacity (Ferrucci et al., 2007).

According to National Institute for Health and Care research (NIHR), 69% of the population has experienced some sort of persistent gut, and gastrointestinal complaints account for 10% of consultations in primary care. Collectively, digestive diseases are also a factor in 1 in 8 deaths in the United Kingdom highlighting the clear need for research in this area. It is very common for people to experience gastrointestinal symptoms, although many of them lack an underlying cause. The majority of these individuals will be classified as having one of several functional gastrointestinal disorders, including functional constipation, functional dyspepsia, and functional irritable bowel syndrome.

Based on frequency data that establishes abnormality, functional GI disorders are differentiated from common GI symptoms. A diagnostic questionnaire that can be used to identify patients with FGIDs for clinical research can be made by determining abnormal and unusual frequencies (Drossman and Hasler, 2016). Up to 40% of individuals in a given moment can have one of these illnesses, and two-thirds of them will experience persistent symptoms that change over time (Black et al, 2020). Epidemiologists have divided the disease burden into important groups, including non-communicable (NCDs), communicable, maternal, neonatal, and nutritional diseases and injuries (Roser and Ritchie, 2021). In 2019, 89 million people worldwide suffered from digestive diseases, according to IHME data which has increased from 84 million in 2016 (Fig 2.1). In India, the graph revealed that 18.5 million people suffered from digestive disorders (Fig 2.2). This information shows a rising graph peak over time, showing a rise in the prevalence of digestive illnesses in 2016 (Global Burden of Disease Study, 2017).

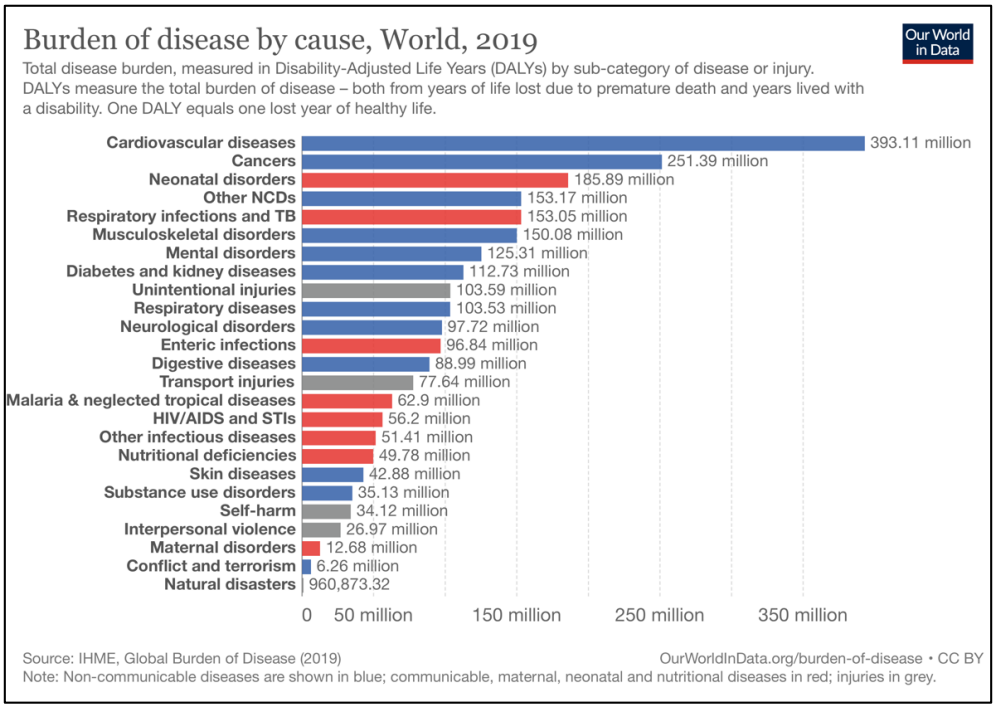

Fig 2.1 : Disease burden by NCD in world.
Source: IHME, Global Burden of Disease,2019

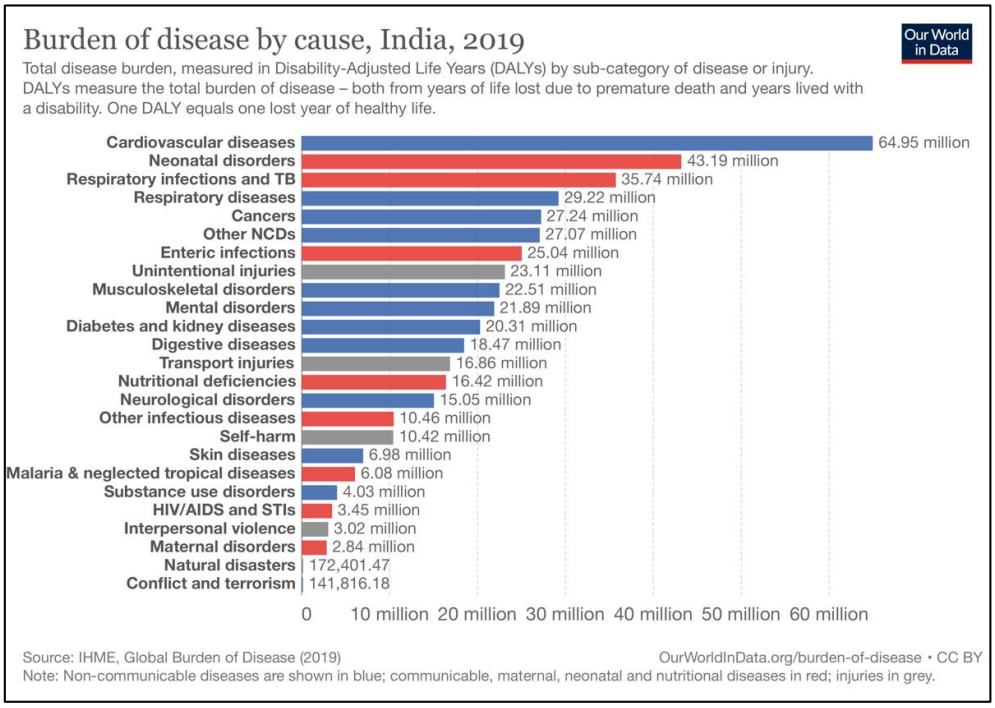

Fig 2.2: Disease burden by NCD in India.
Source: IHME, Global Burden of Disease,2019

Functional gastrointestinal disorders (FGIDs) are an umbrella term of disorders that are only identified by their signs and symptoms, which may include any combination of the following symptoms: abdominal pain, dyspepsia, regurgitation, bloating, constipation, diarrhoea, incontinence, and problems passing food or stools. Functional dysphagia, functional dyspepsia, gastroparesis, irritable bowel syndrome (IBS), functional constipation, diarrhoea, and faecal incontinence are examples of common FGIDs (Mukhtar et al, 2019).

2.1.1. Global and National prevalence of Functional Constipation

According to NICE (National Institute for Health and Care Excellence), constipation is a frequent issue that can affect anyone at any age. The cited prevalence rates fluctuate because study populations and the term "constipation" are defined differently.

FC is a functional bowel condition characterised by symptoms of difficult, irregular, or incomplete faeces. Patients with FC should not fit the criteria for IBS, even though bloating and/or stomach discomfort may be present but are not the main symptoms. Both the beginning of symptoms and their presence during the previous three months must have occurred at least six months prior to the diagnosis (Mearin et al, 2016). Constipation is a digestive system disorder that can cause infrequent stools, difficult stool passage with pain and stiffness, and other symptoms. Acute constipation may cause the intestines to block, necessitating surgery (Benninga et al, 2005).

Global prevalence of Constipation

Chronic constipation causes roughly 1 million hospital admissions each year in the USA. As per Martin et al (2006), constipation places a considerable financial burden on the USA. It's fairly usual to experience constipation. In the UK, chronic constipation is still diagnosed in more than one million GP appointments and 63,000 hospital admissions each year, despite the fact that the majority of sufferers do not seek medical attention.

The total direct medical expenditures connected with the illness were estimated to be US$235 million in 2001, and 95.3% of these costs were incurred from outpatient care. However, limited information is available on the direct medical costs linked to chronic constipation (Martin et al, 2006).

According to the application of Rome criteria, a systematic review and meta-analysis of pooled, population-based cross-sectional studies indicated that the prevalence of constipation varied around the world (Barberio, 2021). Forty five studies out of the 8174 citations assessed met the eligibility requirements, representing 80 different populations and including 275260 individuals. The prevalence of functional constipation was 15 % in studies using the Rome I criteria, 11 % in studies using the Rome II criteria in studies using the Rome III criteria, and 10 % in studies using the Rome IV criteria.

Studies conducted also proved that regardless of the Rome criteria being applied, the prevalence of functional constipation was higher in women (Barberio et al, 2021). According to Emmanuel (2017), constipation affects 33.5% of those between the ages of 60 and 101, making the prevalence more evident in the elderly population. Institutional setting exhibited a higher prevalence.

Constipation has been observed in 30–40% of the population who live in their own homes, in over 50% of nursing home residents, and in about 70% of those hospitalised on long-stay wards. Another study showed that the prevalence of FC in adults ranges from 1.9% to 40.1%, with a typical prevalence rate of about 14%; which also stated that self-reported rates of constipation are higher than those determined by the Rome criteria (Mearin et al, 2016).

Prevalence of constipation in India

Despite the lack of data, studies show that FC is a prevalent health issue in India, debunking the notion that vegetarianism, with its high fibre intake, and higher frequency of bowel movements, makes FC less common and perhaps underreported (Ghoshal et al, 2018) The prevalence of constipation in India is listed in (Table 2.1). Rome II criteria-based constipation prevalence was found to be 16.8% in one population-based study from India, whereas self-reported constipation was found to be 24.8% in the previous year (Rajput and Saini 2014).

In a community research of northern Indians, 555/4767 (11.6%) participants experienced constipation-related symptoms. 4500 non-complaining participants and 2785 patients with chronic lower gastrointestinal problems without an organic aetiology were interviewed as part of a broader pan-Indian multicentric investigation (Fig 2.3).

Table 2.1: Prevalence of Constipation in India (last 10 years)

Author	*Place*	*Sample Size*	*Criteria for Diagnosis*	*Prevalence for constipation*
Goyal et al, 2021	Ludhiana College students	1309	Rome IV Rome III	2.1% 1.3%
Ghoshal and Singh, 2017	Rural UP	2774	Rome III	2.4%
Vidyut Bhatia, 2016	Delhi	1115	Rome II	0.5%
Rajput and Saini, 2014	Chandigarh	505	Rome II Self perception	16.8 24.8
Shah et al, 2014	Western India	128	Rome III	58%
Panigrahi et al, 2013	Odisha	2400	<3 stools/week	2.6

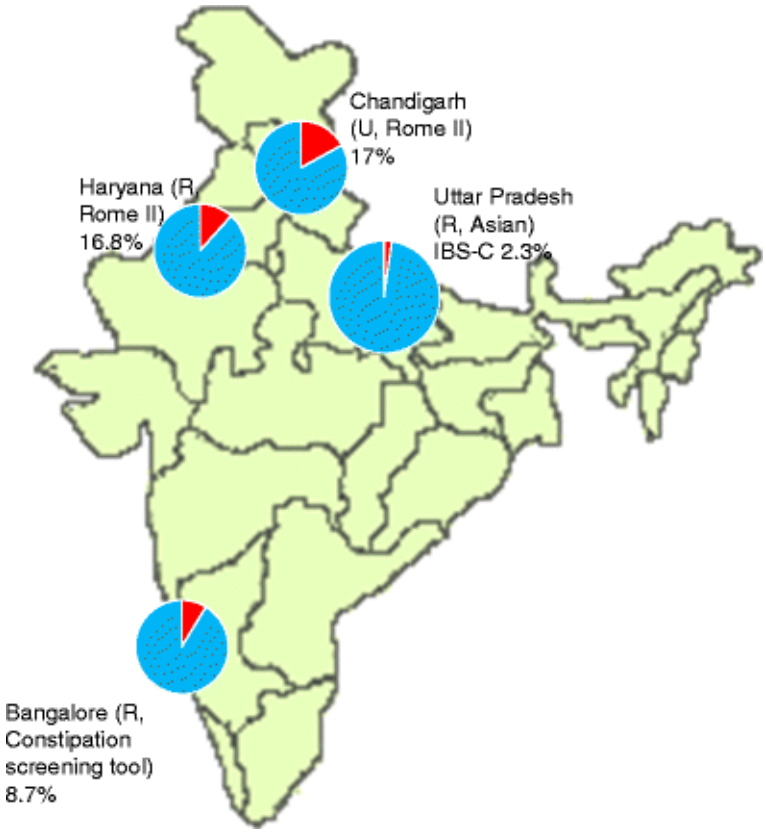

Fig 2.3: State wise prevalence of constipation (Ghoshal, 2017)

In the first group, 1404 people (or 53%) self-reported having constipation, while in the second group, 846 people (or 18%) and 1030 people (or 23%) reported straining at their stools and, correspondingly, incomplete stool evacuation. In a different community survey in rural northern India, 698/2774 (25%) people passed primarily stools of Bristol types I–III, while the prevalence of IBS-C, which is characterised by constipation, was 2.4%. The prevalence of constipation was reported to be 24.8% and 8.6%, respectively, in two smaller community studies from Bangalore and Chandigarh, however the second study was restricted to older people.

Given that chronic constipation rates are greater in older people, the prevalence of the condition is predicted to increase over time as the population ages (Serra et al, 2020). However, due to the significant percentage of people who self-treat rather than seeking medical advice, studies on the prevalence of constipation may understate its actual prevalence (Tack, 2011).

2.2 Criteria to Diagnose Constipation

According to King's College London, previous research have attempted to determine the prevalence of constipation, but their findings ranged from 3% to 35%. The lack of a reliable method to diagnose it may be one cause for this variation. Good care starts with a precise diagnosis of the illness (Dimidi et al, 2019).

Despite being a prevalent disease, constipation is nonetheless challenging to diagnose and frequently unresponsive to therapy. Constipated people exhibit a variety of clinical symptoms that are challenging to categorise objectively, which may contribute to the difficulties in identifying constipation. Furthermore, despite reports that other constipation symptoms, like incomplete defecation, may predominate in constipated people, making a correct diagnosis may be hampered by the fact that deviating stool frequency and deviating consistency are frequently thought of as the easiest symptoms of constipation (Papatheodoridis GV et al, 2010).

The diagnosis of functional constipation benefits from both objective and subjective considerations. Extreme straining is the most prevalent symptom among people with persistent constipation. This symptom is followed by hard stools, soreness in the abdomen, and edema. Constipation can manifest itself in a variety of ways. It is challenging to codify this definition

(Yildirim et al, 2021). Furthermore, the diagnosis of CIC must be made based on clinical symptoms because there are no specific biological markers or tests that can be used to make the diagnosis.

The methods used to identify FC differ greatly. Some individuals self-diagnose, some professionals make pragmatic diagnoses, and some people rely on formal criteria (like Rome IV), which list specific combinations of symptoms that must be present over a predetermined amount of time (Dimidi et al, 2019). Clinical history, physical examination, minimal laboratory tests, colonoscopy or other tests (if clinically indicated and available), and specific tests to evaluate constipation pathophysiology (if clinically indicated and available) should be used in order to determine the diagnosis of FC (Mearin et al, 2016).

The Rome criteria by the Rome Foundation are frequently applied in clinical practise and research (Fig 2.4). They were created in an effort to enhance the diagnosis of constipation. These criteria include subjective symptoms like feeling of anorectal blockage with objective symptoms like frequency of stools. It is crucial to raise the understanding of the significance of these symptoms since doing so would enable a more inclusive and successful method for diagnosing constipation (Verkuijl et al, 2020).

The Rome criteria, which were first created to establish operational definitions for functional gastrointestinal illnesses, are used to characterise FC. ROME IV criteria has been employed in the current study to screen the subjects for the presence of FC. Three Measurements of the prevalence of functional constipation using precise criteria allow for more assured evaluations of its epidemiology (Serra et al, 2020). One of the important observation in the ROME IV Criteria is the type of stool indicated as per the Bristol stool chart. In comparison to self-reported stool frequency, pictorial representations of stool form (Fig 2.5), based on the Bristol stool form scale have been suggested as an accurate method for documenting bowel habits (Saad RJ et al, 2010; Wald A et al, 2008).

Table 1 – Historical evolution of the Rome consensuses and their diagnostic criteria.

Symptoms and diagnosis	Rome I	Rome II	Rome III	Rome IV
Straining to evacuate	>25% of defecations	>25% of defecations	>25% of defecations	>25% of defecations
Lumpy or hard stools	>25% of defecations	>25% of defecations	>25% of defecations	>25% of defecations
Sensation of incomplete evacuation	>25% of defecations	>25% of defecations	>25% of defecations	>25% of defecations
Sensation of anorectal obstruction/blockage	–	>25% of defecations	>25% of defecations	>25% of defecations
Manual maneuvers to facilitate defecations	–	>25% of defecations	>25% of defecations	>25% of defecations
Less than three evacuations per week	Yes	Yes	Yes	Yes
Number of criteria for diagnosis	≥2	≥2	≥2	≥2
Chronological factor	3 months	12 weeks/12 months	3–6 months[a]	3–6 months[a]

[a] Criteria fulfilled over the previous 3 months with symptom onset at least 6 months prior to diagnosis.

Fig 2.4: ROME Criteria over the years

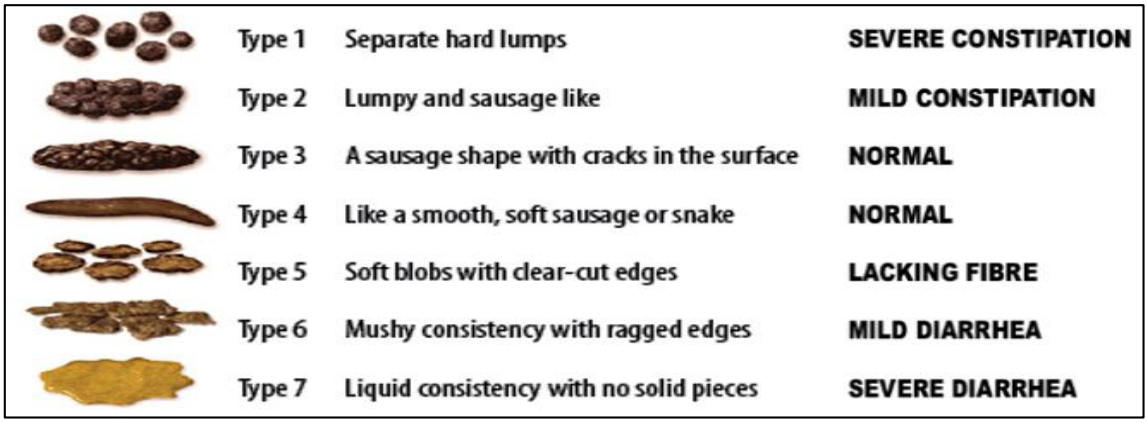

Fig 2.5: Bristol Stool Chart/Scale/Form

2.3 Types of constipation

According to the Rome IV criteria, there are four subtypes of chronic constipation disorders: functional constipation, irritable bowel syndrome with constipation, opioid-induced constipation, and functional defecation disorders, which include insufficient defecatory propulsion and dyssynergic defecation (Aziz et al, 2020). Scientific concepts like secondary reasons (medications), neurological disorders, or systemic illnesses are often mentioned in descriptions of chronic constipation. It is, nevertheless, regarded as primary or idiopathic (Benninga et al, 2005).

Chronic constipation (CC): Symptoms of chronic constipation typically last for at least three months.

Functional constipation (FC): Chronic constipation without a known cause is classified as functional (primary or idiopathic) constipation (Serra, 2017).

A main form of this illness known as chronic idiopathic constipation (CIC), also known as functional constipation (FC), is characterised by symptoms of difficult, infrequent, or incomplete faeces in the absence of any physiological impairment (Ford et al, 2014).
Normal-transit constipation (NTC), slow-transit constipation (STC), and abnormalities of defecation or rectal evacuation can all be classified as FC.
An international panel of specialists categorised this group using symptom-based criteria as follows (Serra, 2020):

- Dyssynergic defecation (DD) occurs when the muscles of the pelvic floor paradoxically constrict or do not fully release.
- Slow transit or insufficient defecatory propulsion refers to a protracted delay in the transportation of faeces through the colon as well as/or weak defecation propulsion.

Colonic transit time can be determined via the stool types 1 and 2, which are linked to slower transit and 6 and 7, which are linked to faster transit (Fig 2.5). Additionally, overlapping dyssynergic defecation (DD) occurs in some FC patients. All cases of FC should be regarded as being under the "umbrella" of FC if there is no indication of structural or metabolic abnormalities to account for symptoms. Diagnostic testing are needed to determine whether someone has a DD or slow transit constipation (Mearin et al, 2016).

Fecal loading/ impaction: Retention of faeces to the point that spontaneous evacuation is unlikely is referred to as faecal loading/impaction.
Fecal incontinence: The condition known as overflow faecal incontinence, also referred to as encopresis or "bypass soiling," is characterised by the leakage of liquid faeces from the proximal colon around impacted stools (Corsetti, 2020).
Irritable bowel syndrome with Constipation (IBS-C): As per Rome IV criteria, patients with IBS-C experiences both loose stools and hard stools (as per Bristol stool chart type 1 and 2; type 6 and7) along with recurrent abdominal pain related to defecation, change is stool frequency and stool form (Fig 2.5).

Opioid-induced constipation (OIC): Opioid medications are known to block stomach emptying and peristalsis in the GI tract, which delays drugs retention and increases fluid absorption. Approximately 40% to 60% of people using opioids who do not have cancer also get OIC (Coyne KS et al, 2015).

2.4 Etiology of constipation

Pathogenesis is multifaceted, focusing on factors such as genetic susceptibility, socioeconomic level, insufficient fibre intake, inadequate fluid intake, immobility or sedentary lifestyle, disruption of the hormone balance or physiological conditions including pregnancy and age, drug side effects, inability to respond to the defecation urge or body structure which causes slow transit or pelvic floor dysfunction, or chrono nutrition profile among others (Benninga et al, 2005). The extensive range and variety of associated factors show how numerous pathophysiological factors contribute to the same symptoms and are frequently not evident in their earliest stages (Forootan et al, 2018). Contrary to other types of constipation, like those with organic causes or those brought on by opioids or other drugs, the root cause of CIC is frequently not well understood.

2.4.1 Lifestyle factors

A healthy lifestyle is advised to lessen the likelihood of adolescent constipation in addition to anecdotal evidence. A study by Yamada et al (2021) showed that during the 3-year period of study, the incidence of adolescent constipation was connected with deteriorating lifestyles such skipping breakfast and leading a sedentary lifestyle. Inadequate calorie intake, inadequate fluid intake or dehydration, change in regular schedule to toilet, inadequate physical activity or immobility, socio-economic deprivation and family history of constipation (Werth et al, 2021; Serra 2020)

According to Werth et al (2021), possible risk factors for functional constipation can be divided into three categories: demographic, lifestyle, and health-related. It is commonly acknowledged that the community's leading risk factors for constipation are a lack of activity, a diet poor in fibre, and insufficient fluid intake (Wald A et al, 2004). According to contradictory statistics, there is no proven association between drinking alcohol and smoking and the occurrence of chronic constipation (Werth et al, 2021). In 2019, disease burden by risk factors worldwide and in India, according to IHME data was published (Fig 2.6; Fig 2.7) which listed various lifestyle factors as a cause for diseases.

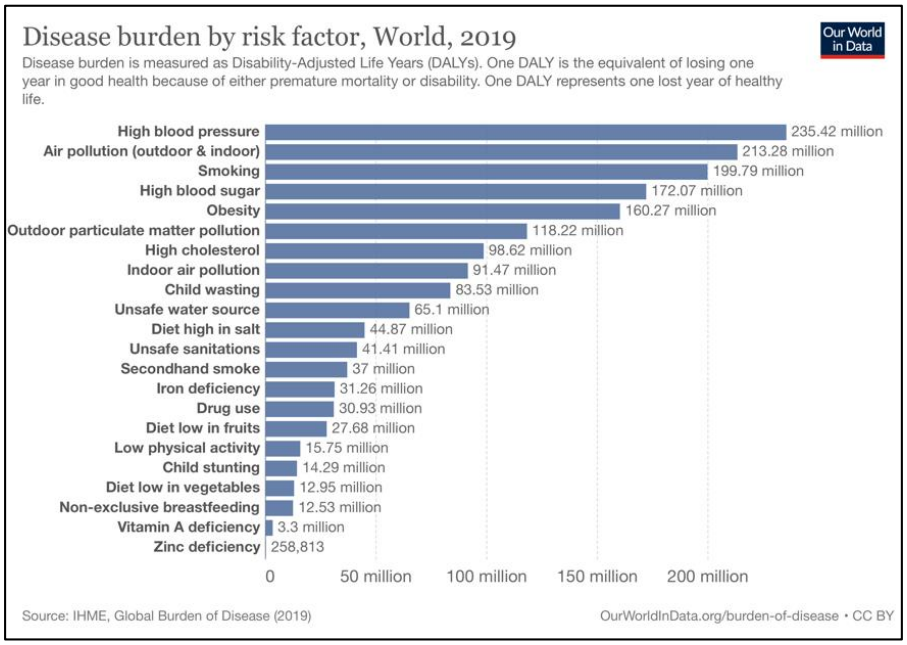

Fig 2.6 : Disease burden by risk factor, World 2019.
Source: IHME, Global Burden of Disease,2019

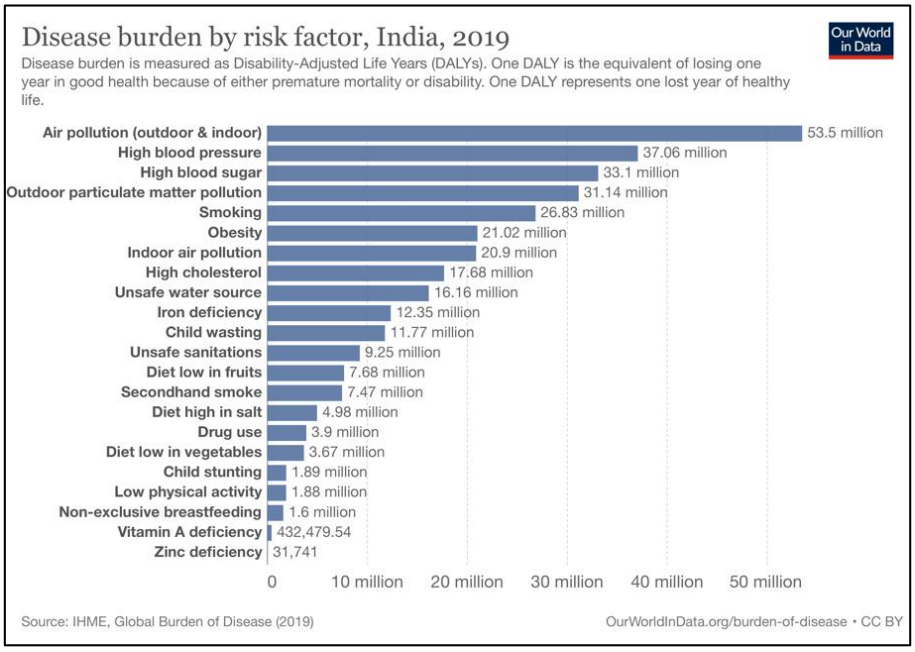

Fig 2.7 : Disease burden by risk factor, India 2019.
Source: IHME, Global Burden of Disease,2019

Chrono nutrition profile as one of the factors

The impact of the biological clock on nutrition, energy balance, and metabolism, which directly affects health status, has become more widely recognised in recent years (Arola-Arnal et al,

2019). Human metabolism and food consumption are synchronised by the circadian rhythm, which has long been understood to be important (Almoosawi et al, 2016). Different foods consumed throughout the day may affect circadian rhythms differently depending on the time of consumption.

This is not just a recent scientific finding; it has been common knowledge for many years (Bravo et al, 2017). Based on the principles of chrononutrition principles, time restricted eating (TRE) is a practical and well-tolerated diet that has multiple beneficial health advantages (Świątkiewicz et al, 2021). Circadian rhythms control a large portion of the physiology of the gastrointestinal tract, including cell growth, motility, digestion, absorption, and electrolyte homeostasis (Voigt et al, 2014).

The "chronotype" of a person influences chrononutrition. A person's chronotype is an analysis of their circadian rhythm that is categorised based on whether they prefer the morning or the evening (Toktas et al, 2018; Henry et al, 2020). An individual's behavioural tendencies are impacted by chronotype (Almoosawi et al, 2019). An individual's ‘morningness’ or ‘eveningness’ is determined by the time of day that they choose to sleep or perform their daily tasks. Individuals who exhibit eveningness are more likely to experience circadian misalignment between their internal circadian clock and their solitary behavioural rhythms, which could make them more likely to have an unhealthy eating pattern and increase their risk of obesity (Eid Bassam et al, 2020).

The relationship between circadian rhythms, nutrition, and metabolism is explored by the emerging area of chrononutrition. Chrononutrition encompasses both the concept of how our internal circadian system is impacted by nutritional composition as well as how food intake timing and biological rhythms affect our health, metabolism, and nutrition (Arola-Arnal, 2019). The effects of biologically active substances can be influenced by biological rhythms, and is also true when these substances are consumed. However, more thorough research is required to verify these effects, comprehend their processes, and determine whether they have any bearing on human health (Aadafer et al, 2020).

2.4.2 Genetic factors

It is still completely unknown how heredity plays a part in the aetiology of constipation. Limited research on the prevalence of constipation among families of individuals with constipation have been reported. Family members of patients with childhood constipation experienced constipation more frequently than those of controls. Patients with genetic disorders typically report having constipation as children. This may suggest that the aetiology of infantile constipation has a strong hereditary component (Peters et al, 2011). With odds ratios of 2.02 for at least one affected relative and 3.99 for at least two, a family history of constipation has been associated to an increased risk. In another research, the authors discovered that a number of clinical attributes, including a younger age of onset and longer duration of symptoms, were associated to a positive family history (Chan et al, 2007).

2.4.3 Psychological factors

According to literature review, anxiety, depression, eating disorders and sexual abuse can contribute as risk factors for constipation (Werth et al, 2021; Serra 2020). Being persistently irritated can be significantly associated with presence of constipation (Yamada et al, 2021).

2.4.4 Medications factors

Antacids, iron or calcium supplements, analgesics including opiates, NSAIDS, antimuscarinics including procyclidine, antidepressants, antipsychotics, antiepileptic drugs including gabapentin, antihistamines, antispasmodics, diuretics (Roque 2015; Wald 2016). This type of constipation is also termed as opioid induced constipation.

2.4.5 Physiological factors

Female gender, advancing age elderly population are risk factors for FC. (Werth et al, 2021; Serra 2020). According to UKTIS (2013), about 40% of pregnant women experience constipation, which is more common than it is in the general population; this may be because to nutritional, physiological, and biochemical changes during pregnancy (Shi et al, 2015).

2.4.6 Medical Illness factors

Endocrine disorders including diabetes (Type 1 and Type 2), hypothyroidism, hypercalemia; myopathic conditions including amyloidosis; neurologic conditions such as autonomic neuropathy, CVD, multiple sclerosis, parkinson's disease, spinal cord injury; structural abnormalities such as fissures, hemarrhoids, colonic strictures, obstructive colonic mass lesions, rectal prolapse, postnatal damage to pelvic floor, intestinal pseudo-obstruction, damaged tissues, diverticulosis, and abnormal restriction of the gut or rectum cause pain during faecal excretion, which prolongs the time it takes for stool to be removed and aggravates chronic constipation; cancer or cancer-related causes of organic stenosis (e.g., colorectal cancer and tumor, intestinal radiation, etc); Anorectal abnormalities, such as anal fissures, strictures, and hemorrhoids. Lupus is a condition of the connective tissues (Roque 2015; Wald 2016).

2.4.7 Other factors

Improper siting position in a toilet seat (Fig 2.8) and difficulty in urge to defecate can be considered as potential risk factors for constipation (Werth et al, 2021; Serra 2020). As per a surveyr conducted by Harvard Medical school (2021), constipation can be facilitated by poor toilet posture, which includes slouching down and having your knees lower than your hips. The anus is somewhat closed in such position, making it more difficult for the abdominal muscles to assist in faeces removal.

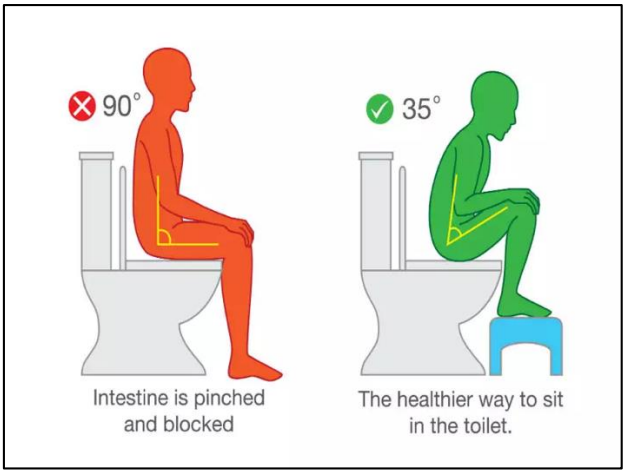

Fig 2.8: Sitting postures on the Western toilet

2.5 Health Implications as a Result of Constipation

Constipation can be a primary challenge brought on by the dysregulation of neuromuscular tissue in the gastrointestinal tract or it can be a secondary disorder brought on by a variety of problems, such as neurologic disease or metabolic disorders (Mearin et al, 2016). Economic and social consequences associated with chronic constipation, which can relate to both chronic idiopathic constipation and functional constipation, can be used to understand the impact of the condition. It is linked to lower health-related quality of life and higher outpatient direct costs (Nag et al, 2020).

2.5.1 Psychological Problems

The significance of psychological factors has been validated by studies on adult constipation. According to a study by Chattat et al. (1996) patients with constipation had more psychological suffering than subjects who were healthy. In patients with constipation, Nehra et al. (2000) discovered a 65% rate of psychological impairment; among all psychological diseases, anxiety, depression, and pain disorders were the most common.

Additionally, other investigations have noted social dysfunction and somatization in people with constipation. Psychosocial factors have an impact on functional gastrointestinal disorders (FGD), according to numerous research. FGID frequently precedes or co-occurs with anxiety, depression, panic, posttraumatic stress, and somatization disorders (Hosseinzadeh et al, 2011).

2.5.2 Impaired Quality of life

World Health Organization (WHO) defines the concept of quality of life (QoL) as an individual's perception of their position in life with respect to their goals, expectations, standards, and concerns. Many functional gastrointestinal (GI) problems, such as faecal incontinence, functional constipation, irritable bowel syndrome (IBS), and others have been researched in relation to quality of life.

Both adult and paediatric patients with FC have regularly been shown to have low physical and mental quality of life (QoL) scores (Wang and Yin, 2015). Although rarely life-threatening, constipation does have an impact on quality of life (Bellini et al, 2017). It has also been used

to monitor changes in patients' wellbeing following laxative therapy in those with chronic constipation (Glia and Lindberg, 1997). The management of constipation improves QoL, according to earlier studies (Dennison et al, 2005).

According to estimates, 70–90% of Americans who experience constipation report uncomfortable symptoms such bloating, straining, and hard stool that last for years and have a detrimental effect on health-related quality of life (HRQoL) (Johanson and Kralstein, 2007). Constipation appears to lower numerous aspects of HRQoL, most notably the psychological element. While the observed changes are similar to those reported for other illness states, it shouldn't be cast off as unimportant. In the fight against constipation, it is crucial to improve quality of life (Yost et al, 2005).

2.6 Approaches to manage and treat constipation

FC is still a clinical problem, with inconsistently effective results from behavioural, conservative, medicinal, and surgical therapies (Corsetti et al, 2021). FC has a mixed prognosis that depends on the underlying etiology (Fig 2.9). Patients frequently need to adjust their lifestyles and take laxatives for weeks or years. According to a study by Bellini et al (2017), 48.5% of the study population (n=878) was suffering from FC for more than 10 years. FC is a fairly prevalent disease in both children and adults, and it is challenging to treat with the therapies that are now available. Currently, roughly 60% of patients taking prescription medicine for constipation report failure, and almost half say they are unsatisfied with their treatment (Science Daily, 2019).

2.6.1 Dietary approaches

According to World Gastroenterology Organisation Global guidelines (2020), to avoid the problem, it's important to follow dietary recommendations like drinking more than two litres of water daily and eating a diet high in fibre (25-30 g/day). Some people react differently to nutritional interventions. There is no single diet that works for everyone, so it is intriguing to think that the microbiome could be able to anticipate how certain diseases will respond to dietary interventions. Nonetheless, individualised nutrition is a worthwhile objective. (Loughman and Staudacher, 2020).

As per literature review, including frequent meals and a healthy, balanced diet with whole grains, sorbitol-rich fruits (and their juices), and vegetables should be important for managing constipation. Apples, apricots, grapes (and raisins), peaches, pears, plums (and prunes), raspberries, and strawberries are among fruits with a high sorbitol concentration (Serra et al, 2020; Serra 2017; Emmanuel 2017).

According to the evidence currently available, general recommendations would include adhering to national healthy eating guidelines that, globally, include recommendations to consume a variety of foods, including those high in fibre (e.g., fruit, vegetables, legumes, wholegrains), and to avoid excessive alcohol intake, substance abuse, and unnecessary pharmaceuticals. They would also include advice to engage in regular exercise, as well as activities that support mental wellbeing and stress management, and to avoid excessive alcohol intake (Loughman and Staudacher, 2020). Increasing the physical activity regime might be a useful approach.

2.6.1.1 Home remedies for treatment of constipation

Stool consistency may be impacted by a variety of food. Chocolate, bananas, and black tea are perceived to cause constipation. A small percentage of persons believed that coffee, wine, and beer softened stools. About 50% of smokers believe cigarettes to soften stools (Müller-Lissner et al, 2005). Ginger is a crucial dietary component that has a carminative action, eases intestinal cramping, lowers pressure on the lower esophageal sphincter, and avoids dyspepsia, flatulence, and bloating (Ali et al, 2008). Triphala has been proven to stimulate hunger, aid regulate hyperacidity, and have good laxative properties. When compared to untreated patients, the treated group showed no negative effects (Mukherjee et al, 2006). Prunes have been successfully used to FC. According to studies from Asia, kiwifruit could alleviate CC symptoms (Chey et al, 2021).

2.6.2 Medicinal approaches

Although there are successful adult trials, up to 50% of people who adhere to the diet are not relieved of their symptoms (Okawa et al, 2019), hence the second line of treatment is the medicinal therapy. FC is typically treated with laxatives (bulk forming agents, osmotic laxatives, and medications modulating motility and/or secretion). Constipation patients are

believed to utilise laxatives in the range of 25–50% of cases, however the majority choose for over-the-counter treatments, and just 10% seek medical attention (Thompson et al, 1997).

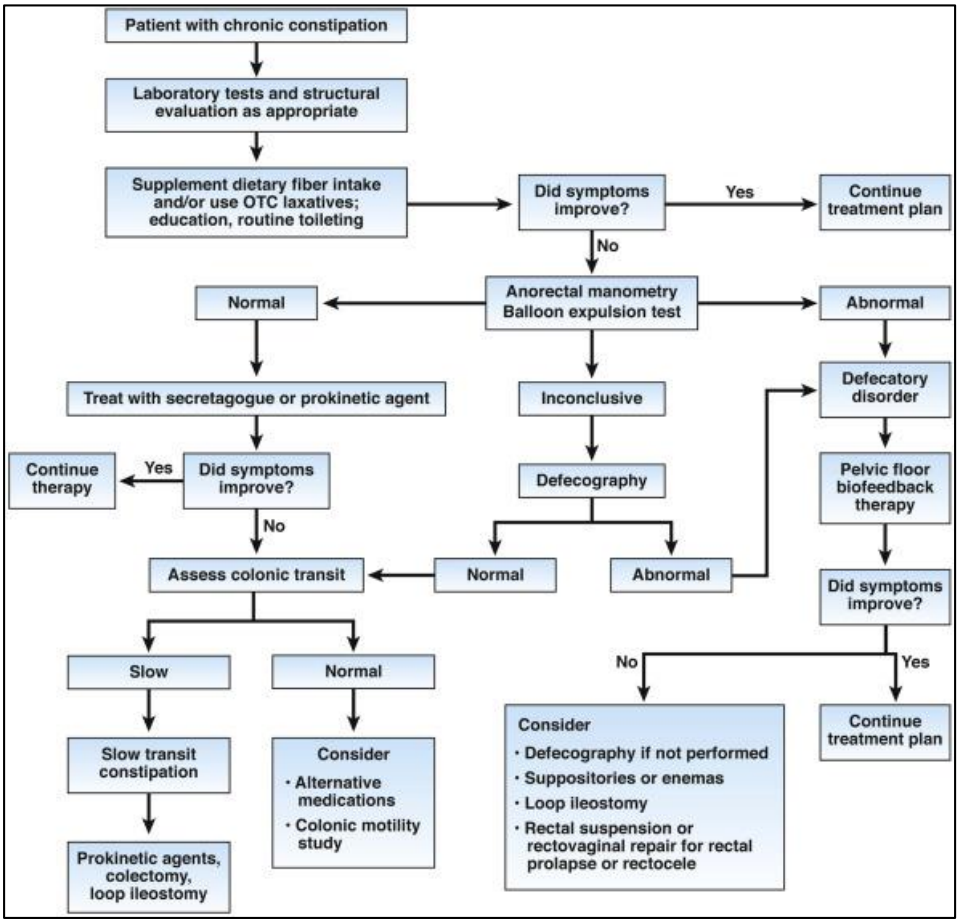

Fig 2.9: Management of Constipation (Corsetti et al, 2018)

As per the study conducted by Serra (2020), providing a laxative that forms a bulk initially, like ispaghula or isabgool, followed by addition or switching to an osmotic laxative, such as a macrogol, if stools continue to be firm or challenging to pass and offering a second-line lactulose therapy if a macrogol is unsuccessful or poorly tolerated. Adding a stimulant laxative might be done if the faeces are soft but hard to pass or a feeling like stomach isn't emptying completely. According to a network comprehensive review and meta-analysis of 21 studies (n=9189), bisacodyl appeared to be superior in terms of the frequency of weekly spontaneous bowel movements. This conclusion was confirmed by a review of 20 randomised placebo-controlled trials, which also revealed that bisacodyl had the highest impact in boosting bowel frequency.

In individuals with FC, a review published in 2020 examined the effects of two isolated fibres, coarse wheat bran and psyllium (or isabgool), on stool output and stool water content (Johnson et al, 2020). According to the research, non-fermented psyllium that forms gel was 3.4 times more effective at increasing faeces than insoluble wheat bran. While psyllium and coarse wheat bran both led to an increase in the water content of the stools, softening them, finely powdered wheat bran had the opposite effect, hardening them.

Bulk-forming laxatives should not be used because opioids hinder the colon from responding with a propulsive action. Instead, they distend the colon and stimulate peristalsis. In rare cases, intestinal blockage and abdominal colic may result from this. Similar to how sugar does, sugar alcohols like sorbitol and lactulose can also cause gas, which can lead to pain and distension in the abdomen.

However, it should be noted that excessive laxative use might result in diarrhoea, which, if it lasts for a long time, can create electrolyte imbalances such hypokalaemia. The longer-term effects of these drugs are unknown, which also raises questions about the safety of long-term laxative use (Lancet editorial, 2019).

2.6.3 Alternative systems to treat constipation including ayurveda, homeopathy, yoga etc

Constipation is a common condition sometimes treated using complementary and alternative medicine. Many people who experience constipation may turn to alternative treatments, partly due to the myth that laxatives are bad for the bowel or "make it lazy" (Corsetti et al, 2020). Before beginning prescription drugs for the treatment of constipation, other treatments include the prescription of fibre supplements, magnesium hydroxide, and olive oil (Silveira et al, 2021).

As per extensive literature review, the studies with treatment involving alternative medicine continued between four and seven weeks, while the follow-up period prolonged between four and sixty-four weeks. The number of weekly spontaneous bowel motions was the main outcome. The patient's satisfaction and clinical symptom score (such as weekly defecation frequency, defecation time, stool features, straining, and stomach discomfort) were the secondary outcomes. The Cleveland Clinic Score, the Quality of Life Questionnaire, and the Bristol Score were all employed in the trials. Indicators of the mechanisms of acupuncture for

constipation, such as plasma motilin, plasma panopioid, and heart rate variability, were also measured (Wang and Yin, 2015; Wu et al, 2014).

In contrast to massage and moxibustion, the literature tend to indicate that acupuncture, electroacupuncture, and herbal therapy are useful in treating constipation. Acupoints on the skin are physically stimulated with needles during acupuncture, an old Chinese Traditional Medicine treatment. Usually, it is referred to as hand acupuncture. Electrical current is applied to needles inserted into acupoints during the practise of electroacupuncture (EA). To advance and demonstrate the effectiveness of complementary and alternative therapy for constipation, more well-crafted research trials are required (Wang and Yin, 2015).

2.6.4 Probiotics

Probiotics are described by the FAO and WHO (2001) as "Living microorganisms that, when administered in adequate amounts, confer health benefits of the host" or "microbially derived factors that stimulate growth of other microorganisms". Probiotics have received a lot of attention recently since they are useful in treating a variety of gastrointestinal problems.

An excellent illustration of the discrepancy between perceptions and evidence about gut health is fermented foods. Although they may have some theoretical benefits, not all fermented foods contain live microorganisms at the time of consumption, and even those that do may not all meet the criteria for probiotic status according to the scientific community. The potential benefits of fermented food organisms for treating gastrointestinal illnesses have gotten very little study attention, despite some indications that they are colonised in the gastrointestinal tract (Staudacher and Loughman, 2021).

With encouraging results, several studies have assessed the effectiveness of various bacterial strains and dosages for the management of FC. However, it is currently impossible to reach firm findings and advise the routine use of probiotics for FC due to the lack of standardisation between the various study protocols and the small sample sizes of the existing trials (Elena et al, 2019).

2.6.5 Prebiotics

According to a study conducted by György et al, (1954), infants who were breastfed revealed a healthy population of Bifidobacteria in their gut. This suggested that human milk contains the 'Bifidus factor'.

Prebiotics are "non-digestible 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, and thereby improve host health," according to Gibson and Roberfroid in 1995. In the human colonic environment, only microbial alterations were taken into account. A more recent definition of a prebiotic was proposed as "A selectively fermented ingredient that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits" (Gibson et al. 2004). Nevertheless, the definition was clarified at the 6th Meeting of the International Scientific Association of Probiotics and Prebiotics (ISAPP) in 2017: "A prebiotic is a substrate that is selectively utilised by host microorganisms conferring health benefit." This was done to extrapolate this into other areas that may benefit from a selective targeting of particular microorganisms. This topic will be dealt in detail in the later part of the chapter.

Functional foods provide basic nutrients and biologically active compounds, which have an overall positive impact on the host's health (Marchand and Vandenplas, 2000). Nutraceuticals like probiotics and prebiotics can be used to make functional food products in levels that give consumers the most health benefits. Prebiotics are non-digestible dietary components that bypass digestion and may improve health by selectively focusing on the growth and/or activity of a limited number of good bacteria in the colon (Gibson et al, 2004).

Consumption of prebiotics can have significant health benefits because of their anti-cancer properties, influence on mineral absorption, lipid metabolism, anti-inflammatory and immune modulating effects (Macfarlane et al, 2013). Prebiotics have shown to improve blood sugar balance in the body and also regulate appetite (Dibase et al, 2008).

Other non-pharmacological approaches

Scheduling regular toilet scenes including encouraging regular and leisurely bathroom use, allowing enough time to ensure that faeces is complete; encouraging people to act right away when they feel the urge to urinate; making sure individuals with limited mobility have the right assistance and space to use the toilet. If the person is shaky on the toilet, making sure they have access to supported seating (Bassotti et al, 2021;Emmanuel, 2017). Another effective approach is retraining of the pelvic floor may be therapeutic in addressing patients with outlet dysfunction (Munshi et al, 2011). For affected people, nonpharmacological treatments offer a practical alternative at an economical cost. General practitioners reported squatting while defecating (using a toilet stool) was an efficient non-pharmacologic treatment for constipation (Sebo et al, 2022)

2.7 Sensory analysis

Sensory analysis is the science involved with the assessment of the organoleptic attributes of a product by the senses. (ISO 5492:2008). A sensory profile is the result of a descriptive analysis of a sample by a panel of assessors. Sensory profiling is the description of sensory properties of a sample, usually consisting in the evaluation of sensory attributes with assignment of an intensity value for each attribute. The attributes are generally evaluated in the order of perception. Some sensory profiles take a view across all of the senses; others (partial profiles) concentrate in detail on particular senses.

Some applications of sensory profiling are as follows: to develop or change a product; to define a product, production standard, or trading standard in terms of its sensory attributes; to define a reference “fresh” product for shelf-life testing; to study and improve shelf-life of a product; to compare a product with a reference product or with other similar products on the market or under development; to map a product's perceived attributes for the purpose of relating them to factors such as instrumental, chemical or physical properties, and/or to consumer acceptability; to characterize by type and intensity the off-odours or off-tastes in a sample

Sensory characteristics includes appearance involving Surface characteristics, Interior appearance, sight (for lightness of foods-transparency, glossy, dullness, opaqueness, turbidity); color; after-taste, flavor which involves odor/ aroma (related to temperature of food), taste

(sweet, salt-tip of tongue and sour-side of tongue and bitter-back of tongue), mouthfeel (composite of sensations) and texture on how they feel on the tongue is characterized by coarse or fine. The concentration required for identification is known as “threshold” for that particular substance.

Sensitivity and consistency have been established by training the panel members. They analyze food products through properly planned experiments and their judgements are quantified by appropriate statistical analysis. Sensory panel is a group of assessors participating in a sensory test. Trained panel members are selected assessors with a demonstrated sensory sensitivity and with considerable training and experience in sensory testing, who are able to make consistent and repeatable sensory assessments of various products.

Different sensory tests are employed for food evaluation including difference test, rating test, sensitivity test and descriptive test. Sensitivity test or thresholds are a specific level below which a compound is not detectable, and above which it can be detected by persons with average sensory acuity. It is defined as a statistically determined point on the stimulus scale at which a transition in a series of sensations or judgments occur.

2.8 Gummies as a confectionery and medium of supplementation

According to a report by Expert market research, Indian market accounts for one of the top vegan food markets in the Asia Pacific region. The expansion of the worldwide vegan food market, which has already reached a value of USD 15.4 billion in 2020, is helping to promote the growth of the vegan food market in India. The market for vegan food is anticipated to expand further from 2022 to 2027 at a CAGR of 26%. The general consensus is that vegan supplements are both healthier and safer than products made with animals. Additionally, prospects for expansion are being created by ethical concerns about the usage of animal components.

Gummies made of active substances are a more advanced formulation strategy. Gummies are available to all age groups without a chewing disorder and dysphagia, much like all other chewable food items. Gummies are chewed, and when saliva is added, they start to dissolve in the mouth. The small intestine, particularly the second half of the duodenum, where the pancreas stores bile acids for fat digestion, would continue this process of dissolution that began in the stomach (Wagner et al, 2019).

A larger market demand for items made with natural ingredients or with a "clean label" has been brought on by the growing interest in useful materials of natural origin. In comparison to other dosage forms, gummy bear food supplements are more palatable to consumers and have less restrictions (Čižauskaitė et al, 2019).

The size of the global gummy market, which was estimated at USD 16.28 billion in 2020, is anticipated to increase at a CAGR (Compound annual growth rate) of 12.6% from 2020 to 2028. Due to the growing number of health-conscious consumers who desire convenient dosage forms of supplements, the market is expanding significantly. Compared to hard pills and tablets, gummies are easier to chew, have a gel-like consistency. Additionally, the product comes in a range of tastes. All of these elements are increasing product demand globally and fostering market expansion (Gummy Market size, 2022).

On the other hand, India is set to be a global leader in nutraceuticals with a market of USD 4-5 billion. By 2025, experts and estimates predict it will increase to over USD 18 billion. In India, the market for dietary supplements is estimated to be worth USD 3924.44 million in 2020, and by 2026, it's expected to be worth USD 10,198.57 million, according to reports. The industry is expanding at a rate of 22% annually (Naresh K, 2021).

A study conducted by Wagner et al (2019) showed that intake of gummies with Vit D3 demonstrated a considerably higher average peak blood concentration (Cmax) values than tablets (gummy: 47.3 ng/mL vs. tablet: 23.4 ng/mL; p 0.0001) in healthy adults. With regard to achieving vit D adequacy, vitD3 gummies exhibited a higher bioavailability than tablets with higher vit D concentrations throughout the trial duration.

2.9 Gut Dysbiosis and Constipation

While thorough research on altering the microbiome through nutrition for better health is encouraging, it is undoubtedly a recent field of study. The term "gut health" is well-used but misinterpreted at times. It is undeniable that gut health is essential for overall wellbeing. Absence of gastrointestinal symptoms (such as abdominal pain, diarrhoea), diseases (such as inflammatory bowel disease, colon cancer), and other unfavourable local conditions (such as increased intestinal permeability, mucosal inflammation, or deficiency (or even excess) of short-chain fatty acids are considered indicators of gut health (Staudacher and Loughman, 2021).

Gut commensal microbiota and pathogenic microorganisms coexist in harmony in healthy people. Intestinal barrier function is compromised when this balance is disturbed (Farthing, 2004). Multiple organ dysfunction syndrome and systemic inflammatory response syndrome are linked to the loss of immunological and intestinal barrier function (Eiwegger et al., 2004). The alterations may be the result of host influence or concurrence from other microorganisms. Intestinal motility, blood flow, secretions, immunity, and the perception of visceral signals are all modulated by microbiota. As a result, it is hypothesised that dysbiosis is crucial to the aetiology of FGID as well as the perception associated with its symptoms (Mukhtar et al, 2019).

Gut microflora dysbiosis is frequently related with bacterial translocation, which is caused by intestinal barrier failure (Putigani, 2014). Dysbiosis may also interfere with the HPA axis; for instance, adrenecorticotrophin (ACTH) and other stress hormones are produced at higher levels in germ-free animals compared to mice with a normal microbiota (Mukhtar et al, 2019).

2.10.1 Overview of Gut environment: A complex ecosystem

With a mucosal surface area of 300 m^2, the human digestive system is quite active. It is made up of a number of intricate organs, from the stomach to the distal colon, which contain 1014 times as many microbial cells as human cells possess in our body (Sekirov et al., 2010). The members of the phylum (family) of bacteria number approximately 50. The Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Fusobacteria, and Verucomicrobia are the most prevalent phyla (Fig 2.10). In order to create effective treatment interventions, it should be helpful to understand the reason or effect of these gut microbiota balances in health and disease as well as how to maintain or restore a healthy gut microbiota composition (Rinninella et al, 2019).

It is recognised that the gut microbiome and other microbiomes interact with human genetics and ethnicity, epigenetic processes, immunological, endocrine, and other systems, as well as environmental inputs including nutrition, medications, and home pollutants that change during a person's lifespan (Loughman and Staudacher, 2020).

It should not be surprising that several companies now provide direct-to-consumer sequencing of the gut microbiota given the countless studies that are published every day regarding the significance of the gut microbiome for diseases including inflammatory bowel

disease, diabetes, and depression. It is feasible to identify the bacteria that live in the gut for a few hundred dollars and a sample of stool, and then use this information to get what appears to be individualised nutritional advice. It is becoming pretty typical within gastroenterology clinics and beyond to hope that sequencing one's gut microbiome may hold the key to diagnosis and treatment when traditional approaches have failed (Loughman et al, 2020).

To advance our understanding of the topic, future studies should examine lifestyle factors, the existence of additional morbidities, dietary habits, and information on the role of the microbiota's composition in constipation (Silveira et al, 2021).

2.10.2 Specific microorganisms of concern in gut dysbiosis

Microorganism populations reside in each of the gastrointestinal tract compartments (Fig 2.10). The colon has by far the most significant prevalent populations because it has a real symbiotic relationship with the host, which is essential for wellbeing and good health (Roberfroid et al 2010). The major bioreactor of the gastrointestinal tract, the microbiota "organ," is distinguished by a genetic content (microbiome) that is more than 100 times larger than the human genome (Putignani, 2014). For diagnostic and therapeutic purposes, identifying specific gut microbes responsible for chronic constipation may be beneficial.

The proximal end of the small intestine is where firmicutes flourish. The distal region (colon and caecum) is ideal for members of the Actinobacteria and Proteobacteria family but not for Bacteroidetes colonisation. A layer in the colon that is abundant in mucin that is similar to complex carbohydrates makes it possible for microorganisms to colonise (Dae-wook Kang et al, 2015). Beneficial and harmful microbes are listed in Fig 2.11.

A few clinical investigations examined the gut microbial populations in FC. Using culture-based methods, Zoppi et al (1998) found that children with constipation had higher colony counts of the bacteria *Clostridium* and *Bifidobacteria*. When obese children with constipation were compared to obese children without constipation, *Bifidobacteria* and *Lactobacillus* were not shown to be significantly different in the stool samples in a recent study using pyrosequencing (Zhu et al, 2014). Contrarily, persons with chronic constipation had low amounts of *Bifidobacteria* and *Lactobacillus* in their stool samples, according to Khalif et al (2000).

There is a positive correlation between *Bifidobacteria* species and slower gastrointestinal transit time in the human intestine. Intestinal barrier failure, which promotes the overgrowth of pathogenic bacteria like *Salmonella, Shigella, Clostridia, Staphylococcus aureus, Candida albicans, Campylobacter jejuni, Escherichia coli, Veillonella,* and *Klebsiella* that secrete proinflammatory cytokines amyloids and lipopolysaccharides, is a major cause of dysbiosis of the gut microflora (Putigani, 2014; Wald 2017).

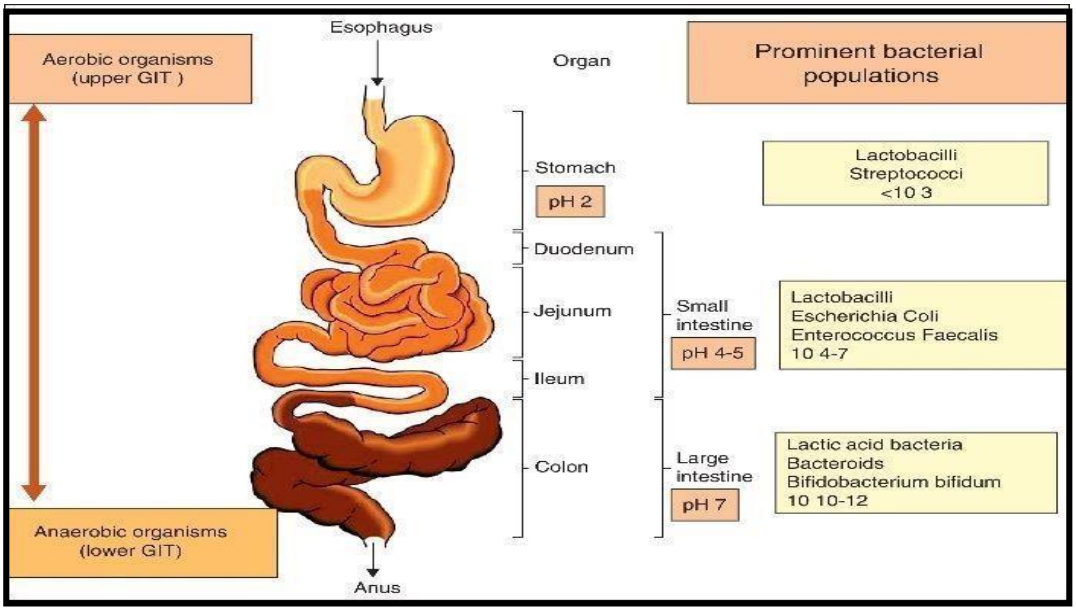

Fig 2.10: Prominent Bacterial population within the human gut (Tojo et al, 2014)

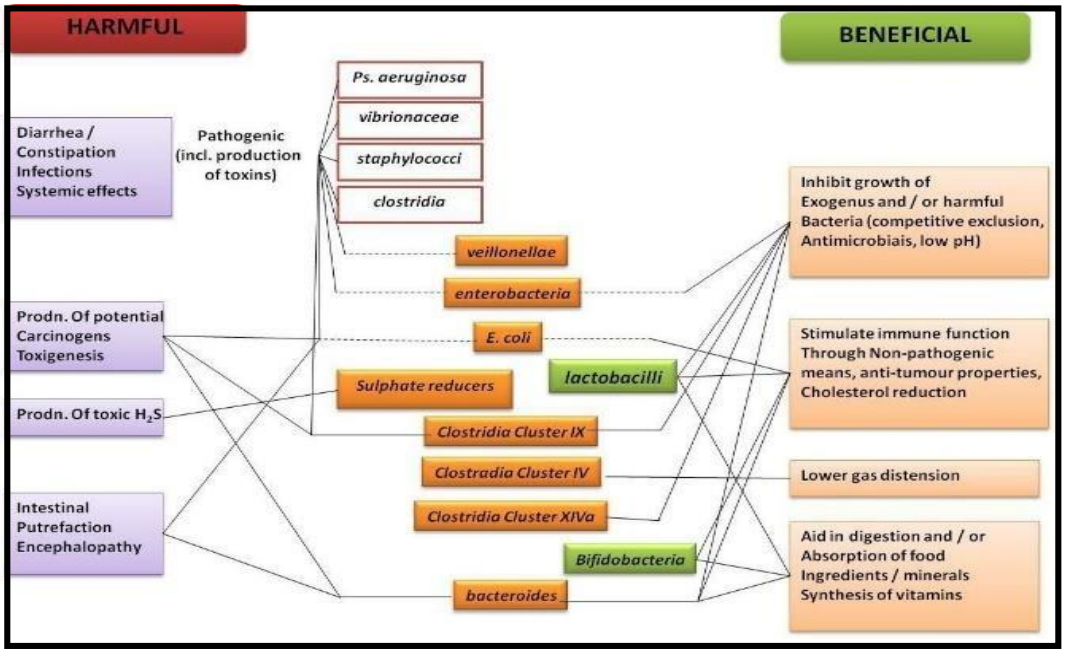

Fig 2.11: Microbial diversity (good and bad) in human gut (Tojo et al, 2014)

Numerous human intervention studies have discovered that eating particular food items can affect the composition of the gut microbiota in a manner in line with the prebiotic notion, and these changes can be statistically significant. As more information becomes available, it will become more widely acknowledged that such changes in the microbiota's composition, particularly an increase in *Bifidobacteria*, can be used as an indicator of intestinal health (Roberfroid et al, 2010).

2.10.3. Gut brain axis

Despite being an ongoing constant in human society, functional GI disorders—better known as disorders of gut-brain interaction—have only recently been thoroughly researched, classified, and treated using well-designed clinical experimental trials. Our knowledge of these disorders adhere to the biopsychosocial model (Drossman, 1998), which is best suited for these disorders in the developing field of neuro-gastroenterology because it lacks a structural foundation to explain its clinical aspects. By altering the gut-brain axis, diet can reduce the symptoms of FGID in two ways: by reducing psychological symptoms and by generating a probiotic-like action (Oriach et al, 2016).

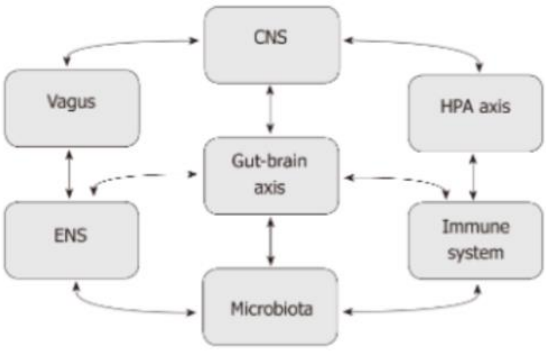

Fig 2.12: Schematic representation of different factors modulating the gut-brain axis (Mukhtar et al, 2019)

Gut microbiota is crucial for the healthy development of the brain and is hypothesised to communicate with the brain both directly and indirectly through the gut-brain axis. The disruption in complex structure of microbes (dysbiosis) can impact the brain and vice versa because of their bidirectional relationship. The intricate mechanisms that drive the disruptions of the two-way communication between the brain and the gastrointestinal system play a

critical role in the pathogenesis and are essential to our knowledge of the disease occurrences (Fig 2.12). The enteric nervous system (ENS), the autonomic nervous system (ANS), the hypothalamus-pituitary axis (HPA), and the central nervous system (CNS) are all involved in the ongoing communication between the brain and the gut. (Mukhtar et al, 2019).

2.10 Alterations in short chain fatty acids profile in constipation

With a chain length of up to six carbon atoms, short chain fatty acid (SCFA) are minuscule organic monocarboxylic acids. Every day, the stomach produces between 500 and 600 mmol of SCFAs, which have an indirect or direct impact on gut-brain communication (Macfarlane et al, 2008). The primary metabolites produced by the microbiota in the large intestine are acetate, propionate, and butyrate, with an approximate molar ratio of 60:20:20, respectively (Pascale A et al., 2018). There are less quantities of production of the other SCFAs formate, valerate, and caproate. By interacting with their receptors on enteroendocrine cells, they encourage the secretion of gut hormones like glucagon-like peptide 1 (GLP1) and peptide YY (PYY), as well as aminobutyric acid (GABA) and serotonin (5-HT), which promotes indirect signalling to the brain via the systemic circulation or vagal pathways.

It has been established, supporting research in adults, that the prebiotic effect includes a major alteration in the makeup of the gut microbiota, particularly an increase in *Bifidobacteria* concentrations in the faeces. This simultaneously enhances the quality of the stools (pH, SCFA, frequency, and consistency), lowers the likelihood of getting gastrointestinal disorders and enhances general health (Roberfroid et al, 2010).

2.11 Galactooligosaccharide as a prebiotic to combat constipation

Galactooligosaccharide (GOS) are a type of prebiotic carbohydrate that have gained increasing attention in recent years for their potential health benefits. Trans-oligosaccharide (TOS) and trans-galacto-oligosaccharide (TGOS) are words that are used interchangeably in the literature for GOS (Fanaro et al, 2005). GOS have also been studied for their potential therapeutic applications in the treatment of various diseases, including inflammatory bowel disease and colorectal cancer. GOS are now widely used as an ingredient in functional foods, infant formulas, and dietary supplements due to their prebiotic properties.

2.11.1 Evolution of GOS as a prebiotic

The evolution of GOS as a prebiotic has been a result of advancements in food technology and research on the gut microbiome. Galactooligosaccharide (GOS) have a long history of use as a prebiotic. GOS were first identified in the 1950s in the whey of milk, and their prebiotic properties were later discovered in the 1980s. Early research on GOS focused on their ability to stimulate the growth of beneficial bacteria, *Bifidobacteria* in the gut. The development of technology for producing GOS in large quantities from lactose in the 1990s led to their widespread use as a prebiotic ingredient in functional foods and dietary supplements. Since then, numerous studies have investigated the effects of GOS on gut microbiota composition, immune function, and intestinal health.

2.11.2 Safety and Tolerance of Galactooligosaccharide (GOS)

According to Commission Implementing Regulation (EU) 2017/24701, GOS manufactured using lactose and microbiologically produced β-galactosidases are permitted to be added to a number of food categories, used as a dietary supplement, and listed on the EU Union list of novel foods. The EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) (2021) raised no safety concerns on the recommended use levels and anticipated intake under the suggested usage conditions of GOS when requested by the European Commission to provide an opinion regarding the expansion of the use of GOS as a novel food (NF) in accordance with Regulation (EU) 2015/2283. The maximum recommended daily consumption of GOS is limited to 16.2 g, which is recommended to be consumed by people in no more than three servings of 12 g/day.

2.11.3 GOS and its functions and health implications

GOS-like oligosaccharides are present in human milk naturally and may help to protect newborn from gastrointestinal pathogenic germs. GOS are composed of galactose molecules linked together in various configurations, and they are not digested in the small intestine, but instead are fermented by bacteria in the large intestine. GOS is made commercially using chicory roots or sucrose and are found naturally in vegetables. GOS refers to a class of carbohydrates made primarily of oligo-galactose with traces of lactose and glucose (Macfarlane, 2009).

Due to the many galactosidic linkages connected, GOS is split into α-galacto-oligosaccharides (α-GOS) and β-galacto-oligosaccharides (β-GOS) (Tian et al.,2019). To date, β-GOS, which is produced by β-galactosidase through the lactose transgalactosylation reaction, has been the most widely used for research and commercial manufacturing (Ekhart and Timmermans, 1996).. There are, however, not many investigations on α-GOS at the moment. According to Dai et al. (2018), the oligosaccharide α-GOS is found in a wide variety of plants.

Currently, the following are the main methods used to produce GOS (Torres et al., 2010):
(1) Using a natural extraction process, whey or lactose are primarily hydrolyzed to produce GOS. GOS has few natural sources, mostly derived from the seeds of leguminous plants, and is missing charges, making it challenging to separate and extract GOS from natural components;
(2) hydrolyzed polysaccharides, which have the drawbacks of a low conversion rate and complex components, making it challenging to obtain GOS products with a high content;
(3) chemical synthesis, where the necessary reagents are toxic and easily contaminated, and the synthesis procedure is time-consuming;
(4) In terms of enzyme synthesis, transglycosidase of β-galactosidase is primarily responsible for the production of GOS.

The primary method for producing GOS at the moment is the enzymatic process, which has the benefits of safety, high efficiency, and little environmental damage. Different microbes can produce β-galactosidase. According to Fewtrell et al. (2007), a number of variables, such as the enzyme source, lactose concentration, substrate composition, and reaction conditions have a significant impact on the synthesis of GOS. Without a doubt, β-galactosidase will mature into a valuable synthetic tool.

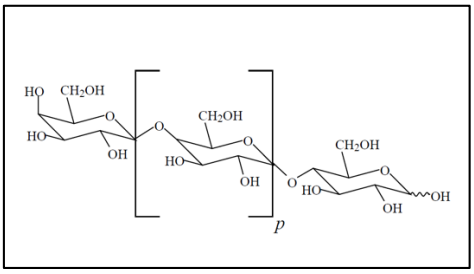

Fig 2.13: Structure of Galactooligosaccharide (GOS)

According to Kimura et al. (2015), GOS is often a colourless, water-soluble substance with a viscosity akin to corn syrup. Due to the presence of β-glucosidic bonds between the moieties, GOS is thermally stable at pH 7. According to Panesar et al. (2018), GOS typically has a lower sweetness that is typically 0.3–0.6 times that of sucrose. As a result, GOS can be used as a filler to a variety of dishes to improve their flavour. GOS is suitable for diabetes patients and low-calorie diets since it has a low caloric content and is difficult for the upper gastrointestinal system to disintegrate. In addition, GOS is very moisturising (Li et al., 2009).

The fermentation of GOS leads to the production of SCFA and other metabolites that can improve gut health and support the growth of beneficial gut bacteria. However, further research is still needed to fully elucidate the mechanisms behind these effects and optimize GOS formulations for maximum health benefits (Zhaojun et al, 2022).

Prebiotics like GOS operate as soluble fibres, which is why they have laxative effects. They enter the colon undigested and are fermented and hydrolyzed by bacteria there. A number of studies have also demonstrated the prebiotic, bifidogenic effects of GOS or a combination of GOS and FOS on colonic flora in both infants (ages 5, 7, and 8) and adults (ages 9–11) (Ben XM et al, 2004). According to some researchers, constipation has been linked to a decrease in Bifidobacteria, therefore treating this issue might be beneficial for bowel function (Hamilton-Miller et, 2004).

As GOS are non-digestible oligosaccharides, gut microflora can utilize them to alter the composition of the gut microbiota (Whisner et al, 2013). A study conducted by He et al (2021) demonstrates that adding GOS to a high-fat diet can successfully boost the proliferation of Bifidobacteria. The majority of *Bifidobacteria* are able to create lactic acid, which can acidify the intestinal environment, stop the activity of pathogenic bacteria from growing, and enhance mucosal barrier performance.

2.11.4 Role of GOS in improving the gut brain axis

Galactooligosaccharide (GOS) have been shown to play a role in improving the gut-brain axis, which refers to the bidirectional communication between the gut and the central nervous system. The gut microbiome is now recognized as an important factor in this communication, and GOS can help modulate the gut microbiome to improve this communication. GOS have

been shown to increase the abundance of beneficial bacteria, such as Bifidobacteria and lactobacilli, in the gut, which can help improve gut health and support the production of neurotransmitters such as serotonin and dopamine. These neurotransmitters are involved in regulating mood, emotions, and behaviour, and their production can be influenced by the gut microbiome.

Several studies have demonstrated the positive effects of GOS on the gut-brain axis. In a randomized, double-blind, placebo-controlled study, healthy adults who consumed GOS showed improved mood and cognitive function compared to those who received a placebo. Another study in rodents found that GOS supplementation led to changes in the gut microbiome and increased expression of genes related to neurotransmitter synthesis in the brain. Additionally, GOS have been shown to reduce stress-induced changes in gut microbiota composition and behaviour in rodents.

Overall, these studies suggest that GOS can play a role in improving the gut-brain axis by modulating the gut microbiome and supporting the production of neurotransmitters. Further research is needed to fully understand the mechanisms behind these effects and to determine the optimal dosages and formulations of GOS for maximum benefit.