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GUT FEELINGS: EXAMINING THE IMPACT OF ULTRA-PROCESSED FOODS ON PUBLIC HEALTH OUTCOMES AND INTERVENTIONS TARGETING THE GUT MICROBIOTA.

Navya Shah Kodaikanal International School

ABSTRACT The adoption of Western diets and sedentary lifestyles has been linked to alterations in gut microbiota, which may be implicated in the heightened prevalence of chronic inflammatory diseases, including diabetes, autoimmune diseases, obesity, depression, and heart disease. Constituting salty and high-fat packaged snacks, confectionery and candied sweets, pastry products, powdered instant noodles, soups, cereals, children's medications and, in some instances, even baby formula – ultra-processed foods (UPFs) pose a mounting public health crisis. UPFs disrupt the overall composition of the Gut Microbiota – promoting inflammation, gut dysbiosis, and negatively impacting cognitive function and processes. This paper reviews the intersections between ultra-processed foods, the Gut Microbiota, and public health issues including food addiction, neuropsychiatric disorders, offspring deficits, obesity and type-2 diabetes. It also synthesises myriad interventions targeting the gut microbiota that can broadly be classified into the categories: gut metabolites, fermented foods and dietary patterns. To the best of the researcher's knowledge, there is very sparse collation on this subject. This paper emphasises the deleterious implications that are brought about by UPFs that are hoped to be taken into consideration while adjusting and framing nutritional policies for proprietary foods.

KEYWORDS : Gut Microbiota; Obesity, T2D; Ultra-processed food; Gut-Brain Axis

INTRODUCTION

Following the industrialisation of food systems, the human diet — including dietary patterns, eating habits and food processing — has seen significant alterations[90]. Consumption of food products with attractive appearances, striking colours, low fat, sugar-free and nutraceutical properties has become increasingly prevalent, especially in western diets[14]. In order to preserve their previously mentioned high sensory qualities and provide a superficial appearance, these types of foods often contain flavour enhancers, artificial sweeteners, emulsifiers, food additives, synthetic colourants, and foaming as well as anti-foaming agents[14]. Having risen dramatically in developing countries across the world, ultra-processed foods account for approximately 50 percent to 60 percent of the daily energy intake in several high-income nations[26].

A High-UPF diet is positively correlated with clinical diagnoses of food addiction, incipient food addiction symptomatology, and relatively high average body fat and cholesterol[39]. A diet rich in fats and sugar, for instance, has been demonstrated in obesity pathogenesis by primarily modifying the gut microbiota diversity and increasing the proportion of gram-negative bacteria rich in endotoxin lipopolysaccharides or LPS. UPF diets, which commonly comprise added sugars, salt, saturated fats, and myriad food additives, may provoke dysbacteriosis, impaired gut barrier operations, as well as disrupt neurotransmitter metabolism in the intestines and brain, therefore impacting the behaviour and functioning of the brain[59].

Apart from being a sensory organ, the gut is an essential component of the enteric nervous system which makes up an extensive section of the autonomic nervous system and comprising roughly 200 to 600 million neurons[46]. The gut microbiota, specifically the metabolites released by the symbiotic microbes (such as SCFAs, lipopolysaccharides, methane, and trimethylamine oxide), are implicated in the aetiology of obesity[145]. With research indicating the gut microbiota's contribution to obesity as well as being involved in insulin signalling and low-grade inflammation, the relationship connecting Type 2 diabetes and the gut microbiota is also becoming increasingly apparent[6].

Globally, obesity and metabolic diseases were predicted to afflict 500 million individuals in 2020. It is essential to evaluate the possible interventions targeting the gut-microbiota given their mediating effect on Obesity, T2D, and other neuropsychiatric deficits that are becoming increasingly prevalent with the overwhelming adoption of Western diets.

To the best of the researcher's knowledge, there is very little collation of research on this. Therefore, this study aims to review the effect of UPF on obesity especially through its effect on the GBA. More specifically, the study addresses the following research questions:

RQ1: What is the impact of ultra-processed foods on the gut brain axis?

RQ2. What is the impact of disruption of the gut brain axis on human health?

RQ3. What are the interventions that can help minimise or mitigate these effects?

The paper is organised as follows. The next section deals with an in-depth literature review about ultra-processed food and its effect on the gut brain axis. The next section discusses the effect of disruptions in gut brain axis on various human systems and processes, followed by some interventions that can help mitigate these effects. Finally, the discussion section provides the practical implications of the study and further scope for research.

The Rise of Ultra-Processed foods and Implications for Public Health

Following the industrialisation of food systems, the human diet — including dietary patterns, eating habits and food processing — has seen significant alterations[90]. Consumption of food products with attractive appearances, striking colours, low fat, sugar-free and nutraceutical properties has become increasingly prevalent, especially in western diets[14].

On the basis of degree and purpose in the modern food industry, the NOVA classification system categorises food items into one of four categories: foods with little to no processing, processed food ingredients, processed foods and ultra-processed foods (UPF). (Gibney, 2019). UPF falls under the bracket of foods that are not typically used in conventional food preparation. These ultra-processed food items include salty and high-fat packaged snacks, confectionery and candied sweets, pastry products, powdered instant noodles, soups, cereals, children's medications and, in some instances, even baby formula[53]. In order to preserve their previously mentioned high sensory qualities and provide a superficial appearance, these types of foods often contain flavour enhancers, artificial sweeteners, emulsifiers, food additives, synthetic colourants, and foaming as well as anti-foaming agents[14].

UPFs have a higher calorie density as opposed to fresh or minimally processed foods (Forde et al.), and they may contribute to a higher energy consumption rate[61]. With a diet rich in UPFs, these properties can lead to energy overconsumption as well as weight gain[26]. Commonly characterised to be high in energy density, fats, sugars, and salt but minimal in nutrients and dietary fibre, UPF has also been linked to an increase the risk of chronic diseases such as obesity, Type 2 diabetes, and cardiovascular diseases[116].

According to an analysis of market sales data from 2007 to 2019, per person quantities of artificial sweeteners in beverages increased 36 percent globally, whereas added sugars in packaged foods increased by 9 percent[132]. Having risen dramatically in developing countries across the world, ultra-processed foods account for approximately 50 percent to 60 percent of the daily energy intake in several high-income nations[26]. Furthermore, such sales of ultra-processed foods have

escalated in tandem with global obesity rates, prominently in middle-income nations[108].

It is worth noting, however, that a high UPF diet poses a mounting public health crisis as it influences energy homeostasis, body weight regulation and metabolism[34]. It may also disrupt the overall composition of the Gut Microbiota – promoting inflammation, gut dysbiosis, and negatively impacting cognitive function and processes from a Microbiota-gut-brain axis frame of reference[144]. A diet rich in fats and sugar, for instance, has been demonstrated in obesity pathogenesis by primarily modifying the gut microbiota diversity and increasing the proportion of gram-negative bacteria rich in endotoxin lipopolysaccharides or LPS. This, in consequence, propels intestinal permeability and LPS translocation from the interstitium to the bloodstream, causing endotoxemia and inducing CNS inflammation[75].

A meta-analysis of prospective and observational studies implicated a correlation between UPF consumption and depression and anxiety symptoms[83]. Moreover, owing to interactions occurring in the MGB axis, a heightened exposure to dietary additives has been associated with behavioural and degenerative neurological disorders including memory and locomotive disorders[148].

Intake of dietary additives including E171, E172, E174 and E175 commonly found in UPF foods is known to instigate gastrotoxicity and hepatotoxicity along with modification of the gut microbiome. It is speculated that the accumulation of the aforementioned additives in the gut and liver following oral exposure paired with their ability to permeate highly selective barriers like the Blood-Brain barrier causes alterations in the brain and the liver[102]. Furthermore, artificial sweeteners contained in UPF products including saccharin, sucralose, aspartame, and acesulfame are suspected to be an etiologic determinant linked to the onset of Inflammatory bowel disease (IBD)[126]. Chronic intake of such sweeteners also caused alterations in hippocampal function and may prove to have deleterious impact on rat cognition[43]. A High-UPF diet is positively correlated with clinical diagnoses of food addiction, incipient food addiction symptomatology, and relatively high average body fat and cholesterol[39]. This may be attributed, in part, to an altered gut microbiota and low-grade gut inflammation induced by the constituent dietary emulsifiers which have been linked to insulin resistance and higher food consumption resulting in higher body weight[17].

Overall, a disruption in the host-microbiota relationship mediated by one's diet can result in a range of inflammatory diseases, neurological and cognitive impairment, metabolic dysfunction, hepatotoxicity, and food addiction pathogenesis.

Despite the growing cognizance of the harmful effects of Ultra-processed foods, such diets remain fundamentally indispensable in our daily lives. Being remarkably palatable, accessible, affordable and conveniently addictive – UPF products are extensively commercialised and distributed in enormous quantities: accounting for a substantial share of many individuals' whole diets, notably in high-income nations[110].

Avoiding consumption of food additives such as dietary emulsifiers, for instance, may prove difficult owing to their pervasiveness in an array of food items including coffee, juice, yoghurt, ice cream and meat based products[118]. Similarly, it may be challenging to avoid food-grade synthetic colourants given their critical function of inhibiting the development of contaminants and preserving the product's optimal pH as well as texture[2].

The Classification of Food Addiction and the Impact of Neuroticism

Food addiction is classified by analogous trends of substance-dependent behaviours towards highly palatable foods[50]. Several studies have used various terms to define Food Addiction (FA) as a substance use disorder including high fat, high sugar (HFHS) foods, refined foods, processed foods, highly processed foods, and ultra-processed foods[120 74 111 138]. FA, manifesting itself in maladaptive dietary patterns, is essential in the pathophysiology of obesity[51].

Given the lack of longitudinal research focussing on FA, *Raymond et al.* postulated that if FA mechanisms are comparable to other Substance Use Disorders, then diagnosing FA in its early stages, i.e. mild or moderate FA, may prove beneficial in minimising the onset of severe FA as well as comorbid chronic diseases like diabetes, hypertension, heart disease, stroke and respiratory concerns[127].

The relationship between FA and BMI is speculated to be susceptible to Neuroticism. Neuroticism is a key mediator in the neuropsychological as well as gut microbial indicators implicated in dopamine synthesis, inflammation, anxiety, and FA. The relationship associating FA and Neuroticism has not been thoroughly explored. However, given its relevance in Bariatrics, it becomes critical to elucidate the underlying principles entailed. The brain-gut-microbiome system serves as one potential fundamental mechanism that may be investigated[60].

A body of evidence has underpinned the idea that neuroticism and psychiatric disorders, including depression and anxiety, can potentially be linked to the changes occurring in the gut microbiome. These alterations have the capacity to influence brain processes and behaviour, chiefly via the neuronal, endocrine, and immunological pathways[90]. Indeed, those diagnosed with food addiction, obesity or a high level of neuroticism exhibited a modified microbial composition, which has been associated with elevated stress and inflammatory mechanisms[60]. Similarly, with regard to neuroticism, it is also important to consider the dysregulation of the hypothalamic-pituitary-adrenal axis (HPA), the body's central stress response system[117]. Identifying mechanisms underlying FA in obesity thus require transdiagnostic approaches that take into consideration extraneous factors. It may also prove advantageous in the innovation of multimodal therapeutic strategies to treat symptoms[164].

FA is not only limited to individuals with obesity, however. Considering the relationship between neuroticism and maladaptive psychological or eating disorders, it is only reasonable to assume that FA also occurs in underweight individuals[64]. Therefore, conflicting variables of psychological and eating disorders, such as emotional eating, must be addressed in order to thoroughly examine the connection between FA and neuroticism[164].

Parental Diet and Offspring Shortfalls

Owing to the shift to sedentary lifestyles and the consumption of manufactured high-sugar, high-calorie, and low-fibre foods, there has been a heightened incidence of obesity in women in their reproductive years[63]. It has been established that maternal obesity, before and during gestation, have both short- and long-term negative health implications that impact the offspring as well as the mother.

Recently published studies conducted across the UK and the US have demonstrated that kids who were born to women having obesity prior to pregnancy had a greater risk of poor cognitive results and autism spectrum disorders (ASDs)[8 124]. Research conducted in rodents too has concluded that a maternal high-fat diet or mHFD causes long-term cognitive impairments transcending multiple generations[134]. Obesity in the mother has been shown to affect the gut microbiome of the child[25], and microbial reinstitution has proven to be effective at reversing the social deficiencies[12].

The gut microbiota, a population of bacteria inhabiting the gastrointestinal (GI) tract that regulate the growth and functioning of the immunological, metabolic, and neural systems, may be a non-genetic yet heritable driver in determining behaviour[22]. The development of this gut ecosystem is presumed to be at or shortly after birth and is stimulated by vertical transfer and interaction with/or absorption of environmental microorganisms[159]. Therefore, the maternal state of nutrition and corresponding interactions are understood to impact the offspring's microbiome and have significant implications for their susceptibility to mental deficits. Indeed, given the recent research linking the gut microbiota to brain functionality, it appears conceivable that such alterations in the offspring gut microbiome, as a result of maternal obesity, may be connected to offspring cognitive deficiencies[92].

In a study by Liu, Xiaoning et al., Students born to overweight or obese Chinese mothers demonstrated significantly lower scores in social subjects and overall school performance, indicating low level of social and learning aptitude. These children also showed poorer cognitive performance and a greater likelihood for ASD as compared to those of children with normal-weight mothers in results that were significant at

the 5 percent level[92].

Maternal exposure to Titanium Dioxide (TiO2) has further been reported to influence learning and memory in offspring. Huang et al. evaluated offspring memory and learning after pregnant rats were administered TiO2 via gavage (100 mg/kgbw) for three weeks. They discovered that the offspring exhibited poor hippocampal cell proliferation along with learning and memory deficits and an impaired spatial recognition memory. Moreover, Heidari et al. investigated the effect of administering TiO2 at 10, 25, and 50 mg/kgbw by gavage to mice over 45 days. They observed that greater dosage of TiO2 not only reduced the amount of tyrosine hydroxylase neurons, a key enzyme in dopamine synthesis, but also augmented dark neurons in the substantia nigra pars compacta, which develop following brain damage and impair the animals' motor abilities[65].

Also, as found by César et al., High-Fat, High-Sugar diet in parents indicated endotoxemia, lowered 'ZO1' gene expression in colon, and decreased serum Ghrelin. Parental HFS diet seems to have an impact on Gut-Brain-Axis programming in male offspring until adulthood, which might be related to increased adiposity later in life[15].

The Relationship Between Neuropsychiatric Health and the Gut-Brain Axis in the Context of an Ultra-Processed Food Diet

Apart from being a sensory organ, the gut is an essential component of the enteric nervous system, constituting an extensive section of the autonomic nervous system and comprising roughly 200 to 600 million neurons[46].

A bidirectional system of communication encompassing the immune, endocrine, and neuronal channels of mechanism across the gut and the brain, the MGB axis facilitates the gut microbiota and associated chemical metabolites to have direct or indirect influence on the brain, thus articulating the system of the gut-brain impact[36].

As a result of the effective link adjoining dysbiosis of the gut microbial populations and behavioural and neurophysical impairment, research has rapidly been gearing towards the development of novel therapeutic approaches targeting the gut microbiota to treat psychiatric illnesses. Whilst there are several factors, including medical status, genetics, and method of birth delivery, that determine the composition of the gut microbiota from infancy to late adulthood, nutrition is thought to be one of the most significant[115].

Regulating the intestinal epithelial barrier, the gut microbiota oversee the absorption of bacterial endotoxins or live bacteria into the bloodstream[10].

A disturbance in the gut microbiome and metabolism triggered by diet or other environmental stimuli can induce dysbiosis, a condition distinguished by an overgrowth of likely pathogenic microbes known as pathobionts[115]. An imbalance of symbionts and pathobionts in the gut can then induce a weakened intestinal barrier function, commonly referred to as leaky gut syndrome along with chronic inflammation. This dysbiosis may also contribute to a number of metabolic and inflammatory conditions, visceral discomfort, as well as disturbances in the central nervous system (CNS) operations[139].Therefore, the connection interlinking the gut microbiota, chronic inflammation and the CNS signifies that gut dysbiosis could influence cognitive function and therefore effectuate behavioural as well as cognitive dysfunctions[27]. An increased intestinal permeability can increase the concentration of lipopolysaccharides (LPS) in the bloodstream, increasing the inflammatory response. Long-term inflammation has also been associated with a variety of neurological conditions, including dementia and depression[155]; As a result, chronic inflammation linked to the microbiota could impact the likelihood to develop such conditions[115].

Changes in the composition of the microbiome may also potentially induce changes in animal behaviour. As an instance, entero bacteriaceae, a broad species of gram-negative bacteria, and Alistipes are more abundant in people with depression than in those without. Faecalibacterium, on the other hand, indicates a negative correlation with indicators of depression[76].

By promoting beneficial bacteria proliferation and inhibiting pathogenic bacteria reproduction, bioactive compounds including polyphenols, which have anti-inflammatory action and neuroprotective effects, retain the ability to inflect microbiota patterns[143].

Neurotransmitters such as dopamine, serotonin, and their chemical precursors are significant in the regulation of energy metabolism, enhancement of behaviour, movement, affect and motivation[47]. The incidence of obesity, food addiction, and psychological disorders including neuroticism, depression, and anxiety have all been affiliated with abnormalities in the aforementioned neurotransmitters or their metabolites, which include tyrosine and tryptophan, among other amino acids[33].

Dietary food-derived chemicals have been postulated to serve as endocrine-regulators promoting the production of intestinal hormones or neurotransmitters in order to increase satiety, alter metabolic pathways, and reduce food intake[144]. UPF diets, which commonly comprise salts, saturated fats, added sugars and myriad food additives, may provoke dysbacteriosis, impaired gut barrier operations, as well as disrupt neurotransmitter metabolism in the intestines and brain, therefore impacting the behaviour and functioning of the brain[59].

A longitudinal cohort study discovered a link between UPF intake and an elevated risk of dementia. A daily 10 percent increase in UPF consumption was found to raise the risk for dementia by 25 percent whereas, replacing the 10 percent UPF consumption with an equal portion of minimally processed or unprocessed foods lowered the risk of dementia by approximately 20 percent[87].

Diets rich in fats and sugar can have adverse consequences on the permeability of the gut and the blood-brain barrier (BBB) integrity[144]. The BBB is distinguished by its highly specialised membrane, which regulates systemic circulation by safeguarding the brain from undesirable compounds.[151] UPF diets, however, have been associated with reduced concentrations of Short-Chain Fatty Acids (SCFAs). SCFAs serve as essential for maintaining BBB integrity and regulating neurotransmitters. SCFAs disruption, on the other hand, may promote intestinal permeability and stimulate inflammatory responses[52].

Long-term HFD consumption reduces BBB integrity[58] and induces an elevated production of pro-inflammatory cytokines including tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and supplementary products of oxidative stress such as malondialdehyde, in addition to low antioxidant efficacy in the brain. The latter point is especially relevant given that brain inflammation and oxidative stress play a decisive part in the onset of neurodegenerative conditions such as Parkinson's disease, Alzheimer's disease, lateral amyotrophic atherosclerosis, and mental health conditions such as depression disorders and anxiety[16].

Numerous investigations have also demonstrated that titanium dioxide, silicon dioxide, silver, gold, and iron oxide nanoparticles are translocated into the bloodstream and can penetrate the BBB in rats and mice, compromising various brain processes[7].

Sweeteners are implicated in obesity and speculated to be linked to other conditions such as neurodegenerative disorders and cancers. A popular artificial sweetener scrutinised for its impact on the neurochemicals and behaviours in the brain, Aspartame is broken down into 50 percent phenylalanine, 40 percent aspartic acid, and 10 percent methanol in the GI tract, affecting the brain's levels of neurotransmitters[72]. The sweetener's use has also been linked to neurophysiological indicators such as mood, learning and cognitive decline. However, these findings remain inconclusive given individual variations, dosage and metabolic activity[23]. Functioning as a chemical agent, aspartame is also capable of raising plasma cortisol levels. Its influence on the composition of gut microbiota also increases the production of corticosterone along with the adrenocorticotropic hormone[24].

Food additives enter numerous tissues via the bloodstream, with the liver having the largest buildup, succeeding the spleen and the kidney. It has also been theorised that nanoparticles can potentially damage the blood-testis barrier and accumulate in the testicles[102]. To elucidate, oral ingestion of silver nanoparticles culminates in long-term memory degradation along with impaired cognitive coordination, disturbing the brain's neuroplasticity[156]. Similarly, as indications of animal

behavioural changes, non-food grade nanosized equivalents of food additives E551, E171, E172, E174 and E175 have been connected to mental health conditions such as stress, cognitive and eating disorders and depression. However, no studies have been conducted to assess the impact of these dietary additives on neurotoxicity or behavioural changes in animals[102].

Several investigations have demonstrated that titanium dioxide, silicon dioxide, silver, gold, and iron oxide nanoparticles are transported into the bloodstream and have the ability to penetrate the BBB in rats and mice, compromising various brain processes[7].

Furthermore, the neurotoxicity brought on by TiO2 nanoparticles has traditionally been attributed to particle accumulation in the brain. Interestingly, the gut-brain axis offers a potential technique to investigate this neurotoxicity, as it has been established that TiO2 nanoparticles disrupt locomotor activity by lowering the diversity and uniformity of the gut microbiota. As a result, enteric neuron excitability is intensified and may travel, through the vagal pathway, to the brain[163].

Additionally, in a 2021 study, children's hyperactive behaviours were reduced when benzoate preservatives and artificial colorings were restricted for a week. Three weeks of drinking beverages containing colourants and sodium benzoate, however, demonstrated a noticeably higher level of hyperactivity[1]. Moreover, emulsifier exposure has been correlated with a rise in anxiety behaviours and a decline in social behaviours in mice[69]. Due to a lack of exhaustive research on the subject, it is inconclusive whether these findings can be extrapolated to humans.

Understanding Obesity

I. In the context of Ultra-Processed Foods

Posing a substantial threat to public health and quality of life, obesity has recently been identified as an epidemic in developed and developing nations[73]. Obesity imposes a major worldwide socioeconomic burden, with a significant share of healthcare expenses resulting from management measures employed to treat obesity-related diseases[63].

Obesity, along with other metabolic diseases including diabetes, hypertension, and nonalcoholic fatty liver disease, is now considered a pandemic in China as a consequence of dietary habits and lifestyle changes[94]. Individual dietary choices are influenced by a myriad of inherent and external variables. Energy intake is influenced by food choices and food cue sensitivity, which in effect, impacts body weight[93]. The adoption of Western diets and sedentary lifestyles has been linked to alterations in gut microbiota, which may be implicated in the heightened prevalence of chronic inflammatory diseases, including diabetes, autoimmune diseases, obesity, depression, and heart disease[167]. Obesity is also regarded as a key predictor of several medical conditions: type 2 diabetes, ischaemic heart disease, cancer as well as stroke[165].

Marked by a high caloric density, salt, fats, and sugars and a lack of dietary fibre and nutrients, UPF has traditionally been recognised as a key contributor to the growth in the prospect of chronic diseases that involve diabetes, obesity and circulatory disease[116]. Consumption of highly processed foods was found to be related with higher BMI and a higher incidence of both excess body weight and obesity after controlling for socio demographics, physical activity and smoking[96].

A principal investigator (PI) implemented one-on-one interviews with each participant of a qualitative research design to gain an understanding of each participant's perspectives, opinions, and attitudes[93] and to learn how they visually perceive food cue images as well as their food preferences while fasting[112].

They discovered that participants' hunger ratings were greater in the presence of food cue visuals of cereals and cereal products (92.86 percent) and sweets (97.14 percent); participants' satiety ratings were greater for milk and dairy products (87.14 percent), cereals and cereal-based goods, and savoury meals (78.57 percent).

Studies have shown that animals administered a high-fat diet (HFD) experience shifts in gastrointestinal function, specifically in the signalling and secretion of GI hormones, which can lead to increased caloric intake, weight gain, and obesity[91]. Research has also demonstrated that transplantation of an obese-type microbiota, brought about by high-fat feeding, into healthy rodents resulted in cognitive disruptions,[11] including a remarkable surge in anxiety-like behaviours while performing in the elevated plus maze, marble burying test and open field[115].

Because our gut microbiota is particularly sensitive to the foods we eat, we are capable of influencing our gut microbiota by our dietary choices[89]. Along with our external environment, our internal environment within the gut has also seen drastic modifications in the previous several decades. Namely, changes in fibre intake, and increased consumption of highly processed, refined and sterilised foods have considerable impact on our gut flora, with potentially unfavourable implications on metabolism and appetite management[63]. Obesity has been closely linked to a microbial diversity imbalance, with Firmicutes outnumbering Bacteroidetes in abundance[143].

II. In the context of the Microbiota-gut-brain Axis

Adult humans possess over ten times the number of microbial cells than the cells that make up the human body[6]. The intestinal microbiota generates a number of metabolites that are intimately connected to several quantitative and qualitative changes and play a role in the pathophysiological facets of obesity and metabolic disorder[125]. It was established that dietary metabolites derived from the gut microbiota govern the liver, adipose tissue and brain via the MGBA, thus promoting the onset of obesity. The gut microbiota, specifically the metabolites released by the symbiotic microbes (such as SCFAs, lipopolysaccharides, methane, and trimethylamine oxide), are implicated in the aetiology of obesity[145].

Such metabolites can lead to long-term inflammatory responses by stimulating calorie intake, lowering the bowel movements, and boosting the accrual of intracellular cholesterol, which can culminate in obesity, insulin resistance, as well as atherosclerosis[32]. Intestinal microbiota-derived metabolites, primarily SCFAs, Bile-Acids and 5-Hydroxyryptamine can be transported to the central nervous system via the immune system, enteric-cerebral nerve system and circulation channels, consequently modulating obesity[143].

Also entwined in the onset of obesity and related metabolic diseases is inflammation[79]. Obesity-associated pathophysiological changes are aggravated by chronic neuroinflammation[149]. According to a substantial body of research, gut microbial dysbiosis is a major contributor in the emergence of obesity and metabolic disorders[145]. Alterations in the composition of the gut faecal flora can result in a disruption of the protective epithelial barrier in the gut wall, leading to the development of intestinal inflammation. This imbalance of the gut microbiota has been linked to the erroneous bacterial translocation into the bowel wall[21]. This translocation of bacteria can modify how the hypothalamus regulates metabolism and appetite through the MGB axis, which can impact body weight[63].

It has also been demonstrated that the neurotransmitter GABA can affect the gut microbiota, intestinal immunity, and intestinal amino acid profiles when administered as a supplement[20]. Additionally, studies have shown that GABA may enhance the quality of sleep[70]; it is also widely acknowledged that obesity has been tied to short sleep duration, evidenced by a number of epidemiological investigations[114] [147].

Type 2 Diabetes

Foods with the labels "sucrose-free," "calorie-free sugar," and "low sugar" are becoming more prevalent as substitutes to appeal to consumers who are health-conscious[144]. Due to their enticing characteristics of cheaper prices, lower calorie consumption, and normalised blood sugar levels, consumption of these non-nutritive/ non-caloric artificial sweeteners has greatly increased in popularity. Chronic non-caloric artificial sweetener intake, however, has been associated in human studies to a heightened incidence of Type 2 diabetes as well as weight gain[150].

With research indicating the gut microbiota's contribution to obesity as well as being involved in insulin signalling and low-grade inflammation, the relationship connecting Type 2 diabetes (T2D) and the gut microbiota is becoming increasingly apparent[6]. According to

Qin et al., patients with T2D exhibited a moderate degree of intestinal microbial dysbiosis, which resulted in a decline in the bacteria that produce universal butyrate and a rise in opportunistic infections[125].

Interventions Targeting the Gut Microbiota

Over the past few years, there has been growing evidence linking the gut microbiota to various diseases, including metabolic syndrome and its associated complications such as diabetes, obesity, non-alcoholic fatty liver disease (NAFLD), insulin resistance, and atherosclerosis[86], inflammatory bowel diseases (IBDs)[4 95], neuropsychiatric traits such as anxiety, depression, and autism,[101] and cancer, including its progression, prognosis, complications, and the effects of radiotherapy and chemotherapy[131].

Bariatric surgery currently serves as the sole therapeutic intervention for obesity that has shown a long-term and consistent reduction in body weight,[154] as well as a decrease in morbidity and death rates[141].

It has also been widely reported that post gastric bypass, a weight loss surgery, a modification occurs in the production of several gut hormones pertaining to appetite, satiety and energy expenditure functions[9 85].

A prospective strategy in treatment is to target the microbiome. Faecal microbiota transplantation has been shown to provide short-term benefits in patients having metabolic syndrome[82]. Consuming fermented foods has also proven effective at alleviating anxiety symptoms in individuals with severe neuroticism[67]. Calorie restriction has been found to promote weight reduction and mood by altering bacterial composition and overall metabolism[99].

I. Gut Hormones

As of now, the only efficacious intervention to combat morbid obesity, with a proven reduction in mortality, is surgery. Although the underlying processes of these surgical procedures are indeterminate, fluctuations in the amounts of gut hormones present in circulation have been revealed to be involved. The alterations in gut hormones including GLP-1, PYY, PP, and oxyntomodulin observed post-operation are presumed to be, at least partially, responsible for the beneficial outcomes of this surgical therapy[154].

Peptide YY or PYY is categorised as a member of the 'PP fold' peptide family, which encompasses pancreatic polypeptide (PP) and neuropeptide Y (NPY). PYY is a peptide consisting of 36 amino acids, secreted by enteroendocrine L cells in the distal gut in response to oral consumption of nutrients. In order to obtain a successful PYY treatment, it is essential to retain stable and consistent quantities of the peptide throughout the term so as to prevent sudden spikes that could induce nausea[154].

Similar to PYY, the **pancreatic polypeptide (PP)** is also a peptide composed of 36 amino acids, secreted following the consumption of food. PP, however, is produced by PP cells situated in the pancreatic islets of Langerhans[3].

PP reduces gastric emptying as well as food consumption,[5] presumably transmitting feedback to the satiety regulating system through the vagus nerve[154].

A peptide hormone that functions as an incretin, **GLP-1** increases the production of pancreatic β cell-produced insulin in response to oral consumption of nutrients. The entero-endocrine L cells of the small intestine constitute the primary source of GLP-1 secretion[66]. GLP-1 also serves as the most effective gut hormone to be implemented for medicinal uses in humans to date. Owing to its incretin action, it has also been employed, with numerous formulations, for the treatment of Type 2 diabetes. In fact, for more than 20 years, the pharmaceutical R&D landscape for Type 2 diabetes has been monopolised by GLP-1-based therapies, particularly GLP-1 analogues and DPP-4 inhibitors[128]. The predominant side effect associated with these GLP-1 receptor agonists is nausea, which renders it challenging to administer stronger doses that may have a more substantial effect on body weight loss[154].

Oxyntomodulin or OXM is a 37-amino-acid peptide hormone which, upon intravenous administration, has been found to suppress both gastric acid production and pancreatic enzyme production, as well as to prolong gastric emptying[136]. OXM has also been shown to dramatically reduce dietary intake as well as body weight gain in rats upon peripheral administration[29]. OXM boosts energy expenditure without having any of the deleterious effects on glycemia that may be expected from glucagon receptor agonism, considering it operates at the glucagon receptor site. As a result of its twofold impact on dietary intake reduction and higher energy expenditure, OXM offers a compelling potential of facilitating the management of obesity[154].

As the only orexigenic hormone known to science, ghrelin enables both lean and obese human subject volunteers to consume more food following administration of the hormone[40 41].The presence of receptors for ghrelin in the hypothalamus, similar to those for PP, PYY, and various other gut hormones, may help elucidate how it regulates appetite[105]. The production of ghrelin increases in individuals who are on restrictive dieting to lose weight or have been diagnosed with anorexia nervosa, whereas they are lower in obese individuals[28].

It would be viable to implement ghrelin as a treatment for obesity if its concentration could be suppressed or its receptor inhibited. Therefore, ghrelin antagonists and receptor blockers have drawn interest for research and innovation as prospective anti-obesity targets[135]. By administering ghrelin immunoconjugates to rats, researchers have also succeeded in developing a "vaccine" that targets the hormone. The results were positive, with an overall decrease in body weight gain and a preferential fall in body fat[166].

II. Probiotics and Prebiotics

Pursuant to a prebiotics expert group, a prebiotic is "a substrate that is used by the host microorganisms selectively in order to confer a health benefit"[55]. Prebiotics can be used directly or indirectly to promote the development of gut microflora[143]. Prebiotics are anticipated to be separated in the future. Fenugreek[81], gold-based nanomaterials[146], compounds made of selenium[113], and pertinent nanoceria are a few examples of prospective choices. The fibre found in diets is a prominent prebiotic renowned for its ability to promote the growth of good bacteria in the colon. For the prevention or treatment for some specific obesity-related diseases, different prebiotic fibres must be preferentially chosen for administration based on their metabolic action in the colon as distinct prebiotics generate differing metabolic substances after microbiota; fermentation[143].

Probiotics are living bacteria that, when given in sufficient quantities, promote the host's health[88]. Probiotics encompass a variety of species which have been heavily studied. Lactobacillus rhamnosus LRH05 substantially decreases white adipose tissue, declines weight gain, and enhances hepatic steatosis along with glucose intolerance[19]. It has also been reported that the probiotic strains Lactobacillus plantarum KY1032 and Lactobacillus curvatus HY7601 coupled show greater efficiency in blocking the gene expressions of numerous of the liver's fatty acid synthesis enzymes, in tandem with drops in fatty acid oxidation-related enzyme function and the corresponding gene expressions[160].

It has also been suggested that "psychobiotics," which are living microorganisms that have a positive impact on mental health when ingested, may hold promise as a therapy for psychiatric disorders by targeting the gut microbiota[37].

Probiotic products' effectiveness has a number favourable facets, including strain- and disease-specificity. Tailoring the strain(s) to the targeted illness in order to develop an adapted individual strategy represents one of the primary criteria in identifying a suitable probiotic[142].

III. Nutrition

Given the strong association between diet and gut microflora, a long-term nutrition disorder can disrupt the individual gut microbiota. A disruption in the gut microbiome interferes with the GBA , causing an aberration in the host's physiology. As a consequence, interventions targeting the diet should be viewed as a major strategy for treating persons with gut microbiota dysbiosis[143].

A number of preclinical studies currently suggests the prospect of treating dysbiosis with dietary modifications for the purpose of bettering cognitive and behavioural results[115]. Gender, age, dietary habits, geographical traits, individual genetic predispositions, and lifestyle choices are only a few of the aspects of the personalised

decisions that people who want to decrease their weight can make[143].

Ketogenic Diet:

esearch has demonstrated that after adopting a **ketogenic diet**, participants experienced a substantial rise in Enterococcus, Anaerostipes, Bifidobacterium, Bacteroides, and Blautia at the level of genus in addition to Actinobacteria at the level of phylum[56]. The ratio of Firmicutes/Bacteroidetes in patients is likewise lowered by the anti-inflammatory and regulatory effects of a Mediterranean diet[49].

Mediterranean diet:

This diet emphasises an array of vegetables, grains, fruits, and mono- or n-3 polyunsaturated fats. It is therefore viewed as the ideal diet for maintaining good health. In a recent study, De Filippis et al. discovered that Italian subjects with a great compliance to the Mediterranean diet had higher levels of short chain fatty acids as well as Prevotella[30]. Contrarily, those with poor compliance had higher concentrations of the substance trimethylamine oxide (TMAO), which has been connected with colorectal cancer, heart disease, and gastrointestinal disorders[115].

Vegetarian diets:

These have been proven effective as a nutritious and therapeutic dietary regimen for a number of chronic illnesses. Vegan diets, on the other hand, may be beneficial in the prevention of both inflammatory and metabolic disorders. Furthermore, they seem to produce a distinct intestinal microbiota profile with lower levels of pathobionts[54].

Fibre-rich diets:

These ameliorate microglial maturation abnormalities and synaptic dysfunction. Diet-derived fibre has been frequently cited to modulate the gut microbiome, presenting a vital substrate to the distal gut microbial colony. Several studies underpin the view that consuming substantial amounts of plant fibres stimulates the proliferation of hydrolytic bacteria and short chain fatty acids and contributes to the diversification of the gut microbiota[31]. Additionally, actinobacteria and bacteroidetes have been observed to positively correlate with high-fibre diets[158]. A study conducted on mice also revealed that behavioural deficiencies, synaptic impairment, and abnormal spliceosome modifications in the offspring were alleviated by increased fibre consumption in the dietary regimen of either the dam or the offspring. Moreover, three different diets high in fibre whole grains, that is, barley, brown rice, and an amalgam of the two, increased the Firmicutes to Bacteroidetes ratio, the diversity of microbes, as well as the abundance of the species Blautia as found in faecal samples[100]. The considerable influence of diet-derived fibres on numerous facets of the host's physiology arise through modifications to the diversity of the gut microbiome[92].

According to research, dietary fibre consumption in the offspring of obese mothers could also potentially restore their microbiome depletion. By altering the gut microbiota and promoting the production of microbial metabolites, a high-fibre diet may be able to prevent behavioural deficiencies in the offspring. Moreover, a modification in the overall composition of the mother's gut microbiota appears to be causally related to behavioural alterations in their offspring[13].

Fermented Foods:

Recent research has postulated that eating **kimchi** could represent an alternate approach for managing obesity. Kimchi is a typical Korean meal made from fermented vegetables. Kimchi offers a substantial amount of functional ingredients including lactic acid microbes (≤ 109 CFU/g) among a range of nutrients that could benefit health, such as minerals, dietary fibres, vitamins, phytochemicals (gingerol, β-carotene, capsaicin, and chlorophylls).[79] Kim et al. determined that kimchi lowers weight gain and minimises neuroinflammation in the hypothalamus area, which regulates appetite and energy expenditure. Furthermore, researchers proved through the use of a gnotobiotic mouse model that kimchi directly increases A. muciniphila abundance in the GI tract and strengthens BBB integrity[79].

CONCLUSION

Overall, research suggests that UPF consumption has a detrimental effect on the gut-brain axis and its function which consequently may contribute to the onset of food addiction and neuroticism, neurocognitive deficits, neurodegenerative diseases, mental health conditions, T2D, metabolic syndrome and obesity. While more research is needed to fully understand the mechanisms underlying the UPF-GBA-obesity link, the available evidence highlights the importance of reducing UPF intake and promoting a whole foods-based diet for optimal health.

The implications of this paper can benefit a wide range of readers, including researchers, healthcare professionals, and dietary policy-makers in the field. This review provides a comprehensive exploration of the current state of knowledge on the connection adjoining UPFs, the Gut Microbiota and public-health implications which allows readers to understand the topic and be wary of its significance given the current surge in Ultra-Processed diets.

Studies in the future should investigate the mechanisms by which food additives and emulsifiers affect individuals' neurophysiological composition via the Gut-Brain axis. Moreover, it is suggested that future research focuses on the long-term efficacy and development of gut-targeted interventions, specifically gut metabolites including GLP-1, PYY, PP, Oxyntomodulin and Ghrelin, given their mediating role in numerous chronic diseases. Studies should investigate the efficiency of combination therapy and the optimal dosage of these gut metabolites and determine pertinent side effects. Further research should also consider the regenerative effects of probiotics, prebiotics and fermented foods via oral administration for their anti-neuroinflammatory effects in alleviating obesity and comorbid conditions.

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