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Dissecting ultra-processed foods and drinks: Do they have a potential to impact the brain?

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Abstract

Ultra-processed foods and drinks (UPF) are formulation of ingredients, mostly of exclusive industrial use, that result from a series of industrial processes. They usually have a low nutrient but high energy density, with a high content of saturated and trans fats, and added sugars. In addition, they have characteristic organoleptic properties, and usually contain sophisticated additives, including artificial sweeteners, to intensify their sensory qualities and imitate the appearance of minimally processed foods. In addition, recent research has warned about the presence of chemicals (e.g., bisphenol) and neo-formed contaminants in these products. UPF production and consumption growth have been spectacular in the last decades, being specially consumed in children and adolescents. UPF features have been associated with a range of adverse health effects such as overeating, the promotion of inflammatory and oxidative stress processes, gut dysbiosis, and metabolic dysfunction including problems in glucose regulation. The evidence that these UPF-related adverse health effects may have on the neural network implicated in eating behavior are discussed, including the potential impact on serotonergic and dopaminergic neurotransmission, brain integrity and function. We end this review by placing UPF in the context of current food environments, by suggesting that an increased exposure to these products through different channels, such as marketing, may contribute to the automatic recruitment of the brain regions associated with food consumption and choice, with a detrimental effect on inhibitory-related prefrontal cortices. While further research is essential, preliminary evidence point to UPF consumption as a potential detrimental factor for brain health and eating behavior.

Keywords: Ultra-processed foods and drinks, Organoleptic properties, Additives, Trans fats, Chemicals, Eating Behavior Brain network.

Abbreviations:

ADI: Acceptable daily intake

BBB: Blood Brain Barrier

BMI: Body Mass Index

BPA: Bisphenol-A

FDA: US Food and Drug Administration

GLP-1: Glucagon like peptide-1

KYN: Kynurenine

LNCSs: Low-/non calorie sweeteners

PHO: Partially hydrogenated vegetable oils

PYY: Peptide tyrosine-tyrosine

SCFA: Short-chain fatty acids

TiO₂: Titanium dioxide

TCS: Triclosan

Trp: Tryptophan

UPF: Ultra-processed foods and drinks

5-HT: Serotonin (5-hydroxytryptamine)

5-HIAA: 5-Hydroxyindoleacetic acid

1. Introduction

Almost all food and drink are processed in some way. Notably, there is to date no clear agreement on which features make a food less or more processed. One of the most used definition devised considers that “ultra-processed foods are formulation of ingredients, mostly of exclusive industrial use, that result from a series of industrial processes” [1]. They contain no or relatively small amounts of minimally processed foods that conserved their nutritional properties. Surimi for example is an imitation of crab meat containing a fish paste made of fish meat (usually threadfin beam, hoki or pollock) which is filleted, minced, washed repeatedly, frozen and mixed with water wheat starch, modified tapioca or potato starch, crab extract and crab flavor, mineral salt, and red colorant. Examples of ultra-processed foods and drinks (in advance UPF) include breads, buns and cakes, cookies, ice creams, chocolates, confectionery (e.g., candies, sweets), breakfast cereals, cereal bars, chips, condensed milk, cheese, fruit yogurts, instant packaged soups and noodles, and savory and sweet snack products in general, and sugared and other soft drinks. Meat products such as nuggets, hot dogs, burgers, and sausages made from processed or extruded remnants of meat are also examples of UPF [2].

In general, most UPF have lower nutrient density, but higher energy density compared to unprocessed foods, being high in saturated and trans fats, added sugars and salt, and are poor sources of protein, dietary fiber, and micronutrients [3, 4]. In addition, UPF usually contain additives, that aim to intensify their sensory qualities and imitate the appearance of minimally processed foods, making them edible, palatable, highly attractive, and habit-forming [1]. Furthermore, recent research has warned about the presence of chemicals in UPF through contact materials such as in the sophisticated packaging (e.g., bisphenol), and neo-formed contaminants generated during food processing practices [5]. Moreover, UPF are designed to be ready-to-eat, sometimes with addition of liquid such as milk, or ready-to-heat, and they are usually encouraged to be eaten in combination (e.g., savory snacks with soft drinks, bread with burger), which fosters overeating.

Emerged in the second half of the past century, UPF production and consumption growth have been spectacular in the last decades. UPF already make more than half of the total dietary energy in some Western countries, such as United States [6], Canada [7] and the UK [8], and between one-fifth and one-third of total dietary energy in middle-income countries such as Brazil [9], Mexico [10] and Chile [11]. Sales are growing in all regions, but most rapidly in upper-middle and low-middle income countries [12].

1.1. UPF and Health

Since the term UPF was coined, there has been an increasing number of studies that have associated UPF consumption with negative health outcomes including overweight, obesity and cardiometabolic risk factors [13, 14], cancer [15, 16], and many other health problems [17–19] in adults. Among children and adolescents, the outcomes include cardiometabolic risks and asthma [20]. Evidence for a causal relationship between the properties of UPF and health outcomes is not clear [21]. Particularly, it remains unclear whether associations can be attributed to the UPF nutrient content, which is shared with many other foods that characterize the Western diet [22], or rather to other more specific UPF features (e.g., additives) [23]. However, preliminary promising evidence supports the causal association between UPF intake and excess weight. A recent systematic review with meta-analysis showed a possible increase in the risk of overweight/obesity, high waist circumference, and the metabolic syndrome across cross-sectional and prospective cohort studies [24]. In congruence with these studies, the first inpatient randomized trial published with 20 weight-stable adults receiving unprocessed and processed diets matched for calories and macronutrients for 14 days showed that the ultra-processed diet led to body weight and fat mass increase, whereas unprocessed diet led to the opposite thus reducing body weight and fat mass over the 2 weeks [25]. The appetite-suppressing peptide tyrosine-tyrosine (PYY) was increased on the unprocessed diet, while the appetite stimulant hormone ghrelin was decreased, suggesting that an unprocessed diet may signal greater satiation than an ultra-processed diet and may hence lead to a decrease in energy intake. The unprocessed diet group also showed improvement of several metabolic comorbidities (e.g., total cholesterol, fasting glucose, insulin). These results suggest that, despite matched calorie and macronutrient content, there may be additional factors in the ultra-processed diet that may lead to unfavorable biochemical markers and hormonal imbalance increasing the risk for elevated body mass indices (BMI) [25].

The attainment of a nutritious, safe, affordable, and sustainable diet is a challenge for all ages, but in children and adolescents is of notable concern. A large study with US youth aged 2-19 years estimated that the

percentage of total energy from consumption of UPF increased from 61.4% to 67.0% between the years 1999 to 2018, whereas the percentage of total energy from consumption of unprocessed or minimally processed foods decreased from 28.8% to 23.5%". Moreover, older children and adolescents had higher UPF consumption from 1999-2000 to 2017-2018 compared to younger children, although this last group also showed an increased UPF intake across time [26]. This is consistent with a higher autonomy and control over their food-related decisions [27]. These outcomes are higher than those estimated in US adults (e.g., a maximum of 59-53.5% of energy intake estimated from UPF in subjects > 20 years old in [6]), and some studies report an inverse association between UPF intake and age [6, 18]. Childhood and adolescence represent key milestones for brain development [28], that culminate with the maturation of the prefrontal cortex and higher executive functions around the second decade [29]. The implication of potential brain insults of UPF intake may be therefore more significant during these sensitive periods, when the brain is particularly responsive to stimuli or insults followed by an extended period of ongoing responsiveness. Notably, accumulating evidence suggest that the protracted plasticity within these late-maturing cortices also confers risk for diverse development psychopathologies [30].

Emerging evidence now highlights the importance of food processing in mental health and eating behaviors with epidemiological data showing an association between UPF intake and the advent of depression in longitudinal studies ([31, 32], see [33] for a meta-analysis), or food addiction traits [34–36], and eating disorders [37] in cross-sectional studies. Also, children with high neophobia more frequently consumed UPF rich in sugar and had a lower adherence to traditional dietary patterns [38]. Notably, the longitudinal study of the population-based birth cohort Generation XXI revealed that higher UPF consumption at 4-7 years was associated with food eating in response to external food cues and the BMI at 10 years [39]. In addition, body image dissatisfaction due to excessive weight in women was also associated with higher consumption of UPF [40]. Besides that, UPF consumption is also associated with unhealthy habits and behaviors. The large Spanish prospective cohort “SUN project”, revealed that those middle-aged university graduates initially not overweight nor obese consuming 6 servings/d of UPF, were more likely to be current smokers, watched more TV, and had the highest prevalence of snacking between meals after 9 years of follow-up [41]. Also, a high prevalence of daily consumption of UPF was associated with TV watching whilst eating meals in children [42], with sedentary behavior in children and adolescents [43], and with anxiety-induced sleep disturbances in adolescents [44].

1.2. Review Scope

In the present review, we aim to provide evidence of the link between UPF consumption and eating behaviors and related functions. To that end, our goal is to first focus on how specific UPF features impact different mechanisms (section 2), to then examine their potential influence on eating behaviors and their neural substrates (section 3) (Figure 1). Although may be mentioned throughout the text, the present review will not encompassed inextricably aspects related to the Western diet that have been reviewed extensively by others [45, 46]. We apologize in advance to our colleagues whose work has been omitted unintentionally and due to space constraints.

2. Ultra-processed food and drinks features

2.1. Intrinsic organoleptic properties

It has been recently hypothesized that UPF effects on eating behaviors are in part related to their organoleptic characteristics. These refer to physical quality attributes of UPF, such as taste and texture that once in the oral cavity would constitute sensory stimuli that is processed orally. Oral signals derived from the taste and texture properties of foods play a role in early, pre-absorptive phases of food ingestion and feedback the brain, modulating satiety and, consequently, food intake [47, 48]. Specifically, the oral processing of food is determined by its taste intensity and the time being in the mouth [49]. Regarding this last point, the soft texture of UPF that makes them easier to chew and swallow may decrease the exposure to orosensory signals leading to lower satiation and increasing eating rate and overall food intake [24, 25, 48]. This suggestion departs from the knowledge that food structure dictates appetite control. Foods with rigid structures (e.g., fiber in plant matter) may require longer chewing time while others may be consumed rapidly [47]. In congruence, increasing the oral exposure to food increases postprandially the incretin glucagon like peptide-1 (GLP-1) and PYY hormones concentrations that suppress food intake [50], while foods that can be ingested rapidly increase

subjective appetite and food intake [51], and the risk to overconsumption [52]. In this line, an interesting study that provided participants with harder and softer versions of a hamburger or rice meals found the soft meal to increase food intake by ~13% [53]. Other studies that also modified food structure changing its textural properties also reported changes in gastric responses, subjective satiety, and the amount of food intake [54, 55].

Furthermore, as mentioned above, taste intensity also affects satiation and subsequent food intake. As part of the Western diet, UPF are usually rich in saturated fat, added sugar, and salt [1]. Data from animal models and humans suggest that dietary exposure to high levels of these substances shifts preference to foods with higher concentrations of these substances [56, 57]. This is thought to happen because these substances reshape the gustatory systems, a mechanism known as chemosensory plasticity. Flies and rodents' studies on sweet taste have shown changes in the transcriptome and epigenome of taste cells and nerves, and the anatomy of the taste system [56]. However, in taste associated gene expression studies conducted with normal weight and obese humans, diet was not monitored [58, 59] and therefore, the effects of UPF on those mechanisms remain to be clarified. Nonetheless, despite the knowledge gaps, substance-induced chemosensory plasticity may affect the processing of taste, and reward processes through interactions with the brain.

2.2. Additives

Food additives are defined as “any substance the intended use of which results or may reasonably be expected to result directly or indirectly in its becoming a component or otherwise affecting the characteristic of any food” [60]. Examples of additives in UPF are sweeteners, colorants, emulsifiers, flavoring agents, coating and thickening agents, and antimicrobial agents. It is under the scope of the present work to provide an exhaustive revision of the impact of each of these additives on health.

Western diets, characterized by increased consumption of UPF and reduced consumption of vegetables and fruits, have long been assumed to promote inflammatory processes and oxidative stress, because of their high composition of saturated fats and refined sugars [45, 46]. Nonetheless, UPF features may also contribute to increase the presence of oxidative stress and inflammation beyond to their fatty and sugary nutrient composition. Laboratory evidence has associated the high content of additives in UPF products with inflammation and oxidative stress [61, 62]. This has been recently substantiated in humans by Edalati and colleagues [63] showing that, compared to adolescents in lower tertiles of UPF intake, those in the higher tertile had a significantly higher mean level of a biomarker of DNA oxidative damage. Higher UPF consumption (>3 servings/day) has also been associated with higher risk of having shorter telomeres in a cross-sectional study of elderly population of the SUN Project [64]. Telomeres are considered markers of biological age, and oxidative stress and inflammation are mechanisms associated with telomere shortening [65]. Moreover, in the trial conducted by Hall and colleagues [66], the unprocessed diet group had reduced inflammation as measured by c-reactive protein compared to baseline, but there were no significant differences in this parameter in the processed diet group compared to either baseline or the unprocessed diet. These preliminary results of the effects of UPF are particularly concerning if considered in line with the evidence that overweight and obese subjects have a reduced production of important antioxidant enzymes [67], and greater synthesis of proinflammatory cytokines [68].

Sucralose, one of the most widely used artificial sweetener, as well as fructose [69, 70], and emulsifiers contribute to the inflammatory cascade [62]. The proposed mechanisms for additives-induced inflammation are not clear. A hypothesis is that inflammatory processes may be promoted by the potential alterations in the gut microbiota and permeability. A very recent *in vitro* study [71] demonstrated that low-/non-calorie sweeteners (LNCSs) at a physiological concentration differentially increase biofilm formation as well as the ability of bacteria to adhere, invade and kill mammalian gut epithelial cells. Notably, gut permeability and deterioration of the epithelial barrier facilitates the absorption of nanosized particles (1-100 nm) contained in some UPF additives which are not metabolized but accumulated in several organs, including the brain [61]. Furthermore, an increased oral absorption of the anticaking/antifoaming silica nanoparticles has been determined in the presence of glucose in an *in vivo* model [72]. In Table 1 the main conclusions of some reviews examining evidence supporting the relationship between UPF additives and gut health are summarized.

Among food additives, sweeteners are the most widely studied. Sweetness in UPF comes not only from caloric sugars (mono-, di- and polysaccharides) but also from artificial LNCSs, such as low sugar alcohols (e.g., sorbitol, maltitol, inositol) and noncaloric sweeteners (e.g., saccharine, aspartame, stevia glycosides) [73]. In

2019, the intake of LNCSs made up approximately two thirds of all ingredients supplied from UPF and soft drinks, with volumes of 25.8, 9.2 and 2.2 kg/capita in high-income, upper-middle income and lower-middle income countries, respectively [12]. With obesity rising on a global scale, LNCSs became a popular sugar substitute, allowing these products to retain their palatability without the associated calories or glycemic effects, while creating the perception of a “healthier product” [74]. However, the consumption of LNCSs is now associated with an increased risk for obesity, metabolic syndrome, and type 2 diabetes [75]. Several hypotheses, not mutually exclusive, might explain the paradoxical association between these “metabolically inactive” LNCSs and their associated adverse metabolic outcomes [76]. Research in this field is complicated by the fact that each LNCSs have different absorption, distribution, metabolism, and excretion profiles [77], making not possible to extrapolate the potential alterations on health of one particular LNCSs to the others [78]. Also, studies differ in the LNCSs dose administered depending on whether they are based on the Acceptable Daily Intake (ADI) levels (the estimated amount of a food additive that can be ingested on a daily basis over a lifetime without appreciable risk to health) proposed by the regulatory bodies in USA or the European Union [75].

One suggested hypothesis is that LNCSs weaken the ability of the organism to predict energy from the sweet taste and therefore evoke the concomitant autonomic and endocrine responses that prepare the digestive tract for the optimal processing of foods (e.g., salivation, gastric acid secretion, insulin release [76, 79]). This is supported by a series of experiments that showed that compared with rats that consume a diet always sweetened with glucose (i.e., caloric), those consuming a diet where the organism was not able to reliably predict calories from sweet taste (i.e., LNCSs) were heavier, accumulate more body fat, and exhibit a diminished ability to compensate for the calories ingested [76]. Furthermore, the LNCSs-induced alteration in glucoregulatory responses to a glucose load, which was associated with reduced circulating levels of GLP-1, was only observed when glucose was given orally, thus tasted, but not when directly released to the stomach, supporting that those disruptions are associated to learned responses elicited by tasting sweetness [76]. To our knowledge, this hypothesis has not been tested in humans, and future research in this area is warranted. A second hypothesis is that LNCSs significantly alters the gut microbiota composition and functioning, with a decrease in beneficial bacterial communities, weight gain, glucose intolerance, and changes in the secretion of short-chain fatty acids (SCFA) [76, 78] (Table 1). SCFA are the main metabolites produced by the microbiota in the large intestine through the anaerobic fermentation of indigestible polysaccharides. They have multiple effects on human health (e.g., butyric acid has anti-obesogenic effects, reducing insulin resistance and improving dyslipemia) and can affect the brain function through a mediational role in the microbiota-gut-brain axis crosstalk. Thus, SCFA might influence brain functioning via direct humoral effects through functional SCFA receptors in the central and peripheral nervous system, indirect endocrine and immune pathways, and neural vagal routes [80, 81]. As for the effects on glucoregulation, Suez et al. [82] showed that exposure to saccharin, sucralose or aspartame induced higher glucose excursions after glucose load than those in control animals not exposed to LNCSs, that could be explained by alterations in the gut-microbiota. In fact, the saccharin-induced hyperglycemia was transferable to germ-free mice never exposed to saccharin through a fecal transplant from saccharin-fed mice, or from microbiota incubated *in vitro* in the presence of saccharin. Similarly, in young healthy volunteers not regular users of LNCSs, one week exposure to the FDA’s maximum saccharin ADI increased glycemic responses to a glucose load test in some of them. Finally, upon results from studies in cell systems and animal models it has also been hypothesized that LNCSs may activate sweet taste receptors in the gastrointestinal tract (e.g., enteroendocrine cells and pancreatic β -cells) and therefore modulate post-ingestive effects also implicated in the glucoregulatory mechanisms (e.g., secretion on incretins such as GLP-1, and insulin) [76].

To our knowledge and according to evidence reviewed and that included in Table 1, additives except sweeteners have been barely evaluated *in vitro*, pure-cell cultures and animal models. Additives including emulsifiers, preservatives, colorants, flavoring, anticaking/antifoaming and coating/thickening agents need further studies, especially in humans, to confirm their impact on gut microbioma and its causal health outcomes. However, several concerns need to be considered to put on track new studies allowing translational application. For instance, humans are widely exposed to additives from different pathways, besides food and beverage consumption. To note, the example of triclosan (TCS), an antimicrobial agent that is banned for food usage in EU and US but found in toothpaste, creams, toys, and clinical use. Exposure to low-doses of TCS (10 and 80 parts per million in diet) promotes low-grade intestinal inflammation, colitis and colitis-associated colon carcinogenesis in mice [83–85].

2.3. Trans fats

UPF are also the main source of dietary trans fatty acids which can also come from natural sources (ruminants) but in little proportion. Industrially produced trans fats are formed in an industrial process that adds hydrogen to vegetable unsaturated oil converting the liquid into a solid, resulting in “partially hydrogenated” vegetable oils (PHO). PHO prolong the shelf life of products, are low-cost, have ability to withstand repeated heating and have better plasticity, which has made their use extensive. They are primarily used for deep-frying and baking, and are the main ingredient in many foods, including margarine, vegetable shortening, and Vanaspati ghee; fried foods and doughnuts; baked goods such as crackers, biscuits, and pies; and pre-mixed products such as pancake and hot chocolate mix. Studies have shown that trans fats disturb the metabolic signaling pathways by adversely affecting lipid levels, triggering systemic inflammation, inducing endothelial dysfunction, and increasing visceral adiposity, body weight, and insulin [86]. Recently, trans fat intake has been shown to cause dysbiosis and associated immune changes in the mice intestine, and significantly aggravated metabolic diseases compared with the intake of normal diet, and these effects were more pronounced than those induced by saturated fat [87].

2.4. Chemicals

Finally, another potential pathway through which UPF features may influence health is because of the presence of neofomed contaminants and contact materials such as bisphenol and phthalates. A positive association between dietary contribution of UPF and urinary concentrations of phthalates and bisphenol has been described in a population-based cross-sectional survey of the general U.S. population [4,93]. The source of these contaminants in UPF is attributed mainly to food production, processing, and packaging practices, food storage conditions and, also animal feeding practices [88, 89]. These chemicals are not bound to the polymer matrix chemically and are known to migrate from food contact materials (plastics, paper, metal, glass, and printing inks) that protect food from physical damage and microbial spoilage [88]. While these chemicals are rapidly eliminated via urinary excretion [90], the omnipresence of exposure sources is of growing concern given that exposure to some phthalates and bisphenol A (BPA) are associated with wide-ranging adverse health outcomes related to their ability to disrupt the endocrine system. Specifically, by binding to hormone receptors, they act as either agonists or antagonists, thus enhancing, dampening, or blocking the action of hormones. They may also alter the number of hormone receptors and the concentration of circulating hormones [91]. Particularly, they have been associated with adverse health outcomes during pregnancy [88, 91], and there is also some evidence that they may increase the risk for diabetes, general/abdominal obesity and insulin resistance [92–94].

UPF may also contain advanced glycation end products (AGEs), such as acrylamide or acrolein, that are produced during the heating and processing of food products through the Maillard reaction between aminoacids and reducing sugars. Cereals, cookies and cakes, biscuits, industrial bread, potato chips and coffee, among others, have been shown to contain a high concentration of acrylamide. AGEs are thought to contribute as risks factors to chronic diseases, such as inflammation and oxidative stress [62,95]. There is experimental evidence that an impaired intestinal barrier permeability may be a mechanism of the AGEs-associated inflammation in microvascular disorders such as chronic kidney disease [96].

3. Do UPF features affect the brain?

We will start this section with a brief review of the main neural networks involved in eating behavior. Then, we will see how the different UPF-related adverse effects reviewed in section 2, may potentially impact eating behavior and the underlying neural substrates (Figure 2).

3.1. Neural network implicated in eating behavior

Classical lesional studies in animals led to the definition of the lateral hypothalamus as the feeding center and the ventromedial hypothalamus as the satiety center [95]. However, the initiation of a meal often can also start as a purely cognitive/executive decision from the prefrontal cortex in the absence of any depletion signal. Similarly, food-associated palatability and pleasantness coded in gustatory, emotional serotonergic (5-HT) and reward dopaminergic (DA) pathways can initiate food intake, even in the absence of hunger [96]. Importantly, homeostatic-hypothalamic and other non-homeostatic brain circuits are strongly interlinked to control food intake [97].

The main portal of entry of energy balance information into the brain is the hypothalamus [98]. Hypothalamic neurons continuously track multiple signals from peripheral energy stores (e.g., leptin and insulin), the gastrointestinal tract (e.g., ghrelin, cholecystokinin, GLP-1, PYY), and short-term meal-related signals (e.g., macronutrients, gut and microbiota-derived satiety signals). However, feeding is also influenced by the organoleptic properties of foods (i.e. taste and texture) which are integrated in the multimodal insula-operculum primary gustatory cortex, thanks to its transmission from the oral cavity through afferent cranial nerves, to the brainstem, parabrachial nuclei, and the gustatory thalamus [99, 100]. In humans, the insular-opercular cortex has showed to code food caloric content, with its activation after food ingestion being associated with plasma concentrations changes of several gut hormones (e.g., ghrelin, insulin, GLP-1) [101]. Insular activity in response to food images is also associated with homeostatic signals, such as peripheral glucose levels [102]. Finally, neuroimaging studies in humans have also shown that the insula-opercular cortex is modulated by higher cognitive functions, such as taste expectations [103]. The anticipation of the subjective hedonic food taste experiences may influence food choice.

As mentioned, brain networks processing food-related homeostatic and organoleptic signals interact with other non-homeostatic circuits, including serotonergic corticolimbic regions such as the hippocampus and the amygdala, the mesolimbic dopamine system, and the orbitofrontal and ventromedial prefrontal areas among others. The hippocampus is mainly involved in coding memory associations with past food experiences, while the amygdala is implicated in assigning hedonic emotional experiences to eating (e.g., pleasantness), as well as in emotion regulation [98, 104]. The striatum, as a key site of the mesolimbic dopamine system, plays a key role in the rewarding properties of foods, and contributes to motivate behaviors towards these foods [105]. Finally, ventromedial and orbitofrontal prefrontal cortices play a key role in food choice, by encoding the subjective value signals from foods [98]. Overall, cumulating evidence has shown that the function in these brain regions favors the preference for habit-based eating behaviors, the consumption of palatable foods, and weight gain [106, 107].

Decision-making in eating decisions also requires the engagement of prefrontal executive-control systems. Prefrontal cortices help in weighing the value of immediate, tempting rewards against potential long-term consequences that may conflict with goals, such as losing weight and leading a healthy lifestyle. The up-regulation of the lateral prefrontal cortex reduces the desire for tasty or craved foods [108, 109]. Indeed, successful weight loss (i.e., at least 10 pounds for at least 1 year) is also associated with greater prefrontal cortex activation when viewing high-energy food stimuli [110]. Some studies have shown that avoidance to select unhealthy-but-tasty options is because the lateral prefrontal cortex downregulate the activity of ventromedial prefrontal cortex sections, while prefrontal cortex damage has been associated with cravings for foods high in refined sugars [98].

3.2. Impact of UPF-related mechanisms into the brain and eating behavior

3.2.1. Neurotransmission

A variety of neurotransmitter systems contribute to our everyday eating choices [111–113]. DA and 5-HT are among the neurotransmitters most studied because of their roles in reinforcement and motivation, and mood and cognition, respectively. Disturbances in these systems have been repeatedly associated with problems in eating self-regulation and an increase in habitual and inflexible unhealthy food choices [111, 112].

The promotion of inflammatory processes associated with UPF features may compromise DA and 5-HT neurotransmission [61–64, 112]. For instance, increased peripheral inflammation is known to alter the metabolic fate of tryptophan (Trp), with a shift towards the kynurenine (KYN) metabolic pathway [112]. Peripheral Trp availability reductions determine, at least in part, a lower brain synthesis of 5-HT. Also, an increase in the KYN metabolic pathway may implicate a simultaneous production change of other KYN-based neuroactive metabolites from glia cells, involving the kynurenic and quinolinic acids which have neuroprotective and neurotoxic effects, respectively [114]. An increased ratio of quinolinic/kynurenic and KYN/Trp have been linked to mental illness, including poor stress coping abilities in depression and cognitive impairment [115, 116]. Such mental difficulties are highly present in individuals with eating disorders and obesity [104, 117], which are also characterized by consuming a notable amount of UPF [24, 35–37].

Moreover, some studies showed that bisphenol exposure leads to a dysregulation in the transcription of genes associated with DA and 5-HT neurotransmission [118–120]. Particularly, it has been hypothesized that alterations in Trp metabolic functioning in the placenta may affect the appropriate 5-HT-related regulation of the developmental programming of the brain through maternal-placental-fetal interactions [121], underling the translation into abnormal behaviors in adulthood. In addition, UPF-effects on gut dysbiosis (Table 1) may also affect eating behaviors through induced alterations in brain neurotransmission, as evidenced by a study showing that germ-free mice have a significant alteration in 38 of the 196 metabolites, with approximately 10 of them known to be involved in brain function, including DA and Trp [122]. Similarly, the attenuation of pro-inflammatory factors elevated Trp and 5-HT precursors in rats following treatment with Bifidobacteria [123]. A more specific evidence of the effect of UPF products is a study showing that 6-months consumption of sucralose in drinking water in mice altered the host microbiota and related metabolites, in particular the ones belonging to the Trp metabolism (i.e., quinolinic and kynurenic acids) [69]. Finally, higher doses or exposure to certain nanoparticles in mice have been also associated with induced impairment in DA and 5-HT neurotransmitters [124, 125], although further studies should explore whether food-grade nanoparticles have similar effects. Also in relation with gut microbiota, SCFAs regulate the expression levels of the enzymes involved in the synthesis of 5-HT and DA, therefore also producing an effect on brain neurochemistry [80].

3.2.2 Brain integrity

Several studies in animals have demonstrated that the inflammatory effects associated with high-fat and Western diets have consequences on BBB permeability. There is evidence of alterations in tight junction proteins vital for maintaining the integrity of the endothelial cells [126], and for the activation of microglia and astrocytes that in turn promote neuroinflammation through cytokines production [127, 128]. Regarding to the specific potential effects of UPF, some indirect evidence come from additives. Specifically, the exposure to non-food grade nanoparticles counterparts indicates that they are translocated into the blood stream and can cross the BBB in mice and rats, disturbing several brain processes [61]. For instance, titanium dioxide (TiO₂) nanoparticles accumulate and cause cytotoxic effects in glial cells, and hippocampal and dopaminergic substantia nigra neurons, which are crucial for memory, learning and locomotor processes [124, 129, 130]. Silver nanoparticles also accumulate in brain [131] and impair short- and long-term memory [132]. These nanoparticles are linked to certain additives that are used in UPF as colorants and antimicrobial agents, although validated methods are needed to size and quantify their presence [133].

Bisphenols and trans fats have also been documented to impact brain integrity and function. Bisphenol-related effects on the developing brain are well documented [134]. For example, BPA can cross the placental barrier and has been postulated to adversely affect ongoing neurodevelopment, ultimately leading to behavioral disorders later in life, including anxiety and hyperactivity [135]. It has been repeatedly shown that developmental exposure to BPA disrupts sexually dimorphic endpoints, including some areas of the hypothalamus and the amygdala-hippocampal complex. Although in adults, BPA is generally thought to be rapidly metabolized [136], it is suggested that longer presence and persistence of bisphenols dose in the circulation may allow for further contact with brain tissues [137]. Further studies should investigate the contribution of UPF intake to elevated BPA exposures. This is of interest to understand bisphenols contribution to obesogenic effects in humans, as a widespread presence of bisphenols in the hypothalamus has been found in human samples [92].

Regarding to trans fats, the greatest danger comes from its capacity to distort the composition of brain membrane phospholipids which modifies the ability of neurons to communicate [138]. Trans fat intake during pregnancy and lactation in rats was related to increased oxidative stress and proinflammatory cytokines in brain areas of the offspring, including the hippocampus and the cortex, and influence memory and anxiety behavior [138–140]. There is also some supporting evidence for a possible role of trans fats in the development of Alzheimer disease and cognitive decline with age, as well as depression risk [141, 142]. This is supported from chronic feeding of saturated and trans fatty acids at high levels in laboratory animals increased A β aggregation, and reduced glucose utilization in key brain regions [141].

Finally, a growing body of studies suggest that gut microbes have an important influence on the BBB and brain integrity through alterations in the production of SCFA and the promotion of inflammatory states ([80, 143], Table 1).

3.2.3. Brain function

It has been argued that the repeated intake of highly palatable high-sugar foods causes functional adaptations in several brain areas key in eating modulation. This is supported by studies such as a randomized controlled trial with healthy individuals in which the daily consumption of high-sugar (31g) beverages down-regulated the striatal response during the intake of that beverage [144]. Congruently, another study showed that frequent ice-cream consumption was associated with a reduced response to milkshake receipt in reward-related brain regions, independent of body mass index [145]. Decreased responsiveness in this motivational-dopaminergic circuit has been associated with habit-based food decision making (e.g., compulsive eating, [146]), and with attenuated sensory satiety (i.e., decline in pleasantness associated with a food as it is eaten). The substance-induced chemosensory plasticity discussed in section 2 is hypothesized to contribute to the decrease in sensory satiety.

On the contrary, preliminary evidence suggests that LNCSs may not appropriately regulate the brain network involved in appetite and reward to process sweet taste. This has been suggested to prompt an extension of the meal episodes to match the expected energy needs through induced variations in the expected signals received by the brain [147, 148]. Findings in healthy samples support that the sweet taste in the absence of nutritive carbohydrates may not lead to hypothalamic changes that are typically linked to satiation [149, 150]. The study of van Opstal and colleagues [151] expanded this initial evidence by showing that unlike glucose and fructose sweetened fat/protein milkshakes, the ingestion of those sweetened with sucralose and allulose had no effect on the functioning of several brain areas, including the insula, and reward-based regions such as the ventral tegmental area and the nucleus accumbens. Indeed, a negative correlation between artificial sweetener use and amygdala (trend for the insula) response to sucrose ingestion has been reported [152]. A lack in the activation of the insula was also observed after the consumption of a standardized meal accompanied with a non-nutritive sweetened drink vs a sucrose-sweetened drink, with those in the first condition also showing higher total energy intake in a subsequent *libitum* buffet [153]. However, in another study with intensive consumers of sugar-sweetened beverages, 3-months replacement with artificially sweetened beverages did not induce changes in the insula or other brain regions subserving reward attribution to the sight of palatable food images, but a pre- to post-intervention decreased activity in prefrontal regions, which was associated with weight loss failure [154].

However, which of the mechanisms that are potentially impaired by LNCSs consumption (e.g., glucoregulation, production of SCFA, inflammation, Table 1) have a major impact on the dysfunction of this brain network requires further research. In addition, further studies may investigate whether the gut dysbiosis associated with UPF consumption promotes affective dysregulation and mood disorders. As SCFA products modulate the hypothalamic-pituitary-adrenal axis, modifications in gut microbiota could lead to depressive symptoms, and dysbiosis followed by decreased SCFA levels play a role in the inflammation process related to the development of depression [80, 81].

4. Sirens from Food Marketing: Warns to Mental Health

Despite the above reviewed negative-health effects attributed to the consumption of UPF and the enacted policies designed to mitigate them [155], their consumption continues to be on rise [12]. Several aspects of the food environment have been suggested to also play a role in the continuous UPF consumption growth, with marketing exerting a powerful influence, especially on the children and young adults' eating patterns [155, 156]. Food marketing comprises any form of commercial advertising that is designed to increase the recognition, appeal, user convenience, and/or consumption of particularly foods [157]. The omnipresence of UPF products through multiple channels [158], including modern food retailers [159], increase its salience among other healthier food options by capturing our attention. Food advertising provides the essential link between UPF and the creation of demand for these products. There are four times more advertisements for foods/beverages that should not be permitted than for permitted foods/beverages in the top five hour timeslots for children [160]. Notably, to date, food advertising almost exclusively promotes UPF. This is concerning if considering suggestions that the onslaught of appetizing food images derived from the increased exposure to digital food images, such as food advertising, may activate the brain mechanisms associated with food consumption in a manner that is relatively automatic [161]. The scientific research have substantiated this by

showing that imaging the sensory properties of favorite [162] and appetizing foods [163] change the activity in some brain regions, including the insular-opercular gustatory processing areas, caudate and hippocampus. Indeed, the view of culturally familiar food advertisements or logos (e.g., McDonalds, Rice Krispies, Coke) may also play a role in attracting consumers' attention and generate vivid representations of the food sensory characteristics, as well as conceptual associations that come easily to mind (i.e., false health appearance). In congruence, studies assessing the brain response to food advertisements or logos have shown consistent activations mostly involving brain regions related to visual processing and attention (i.e., visual cortex, fusiform gyrus), emotional and motivational aspects (i.e., the orbitofrontal cortex, the anterior cingulate cortex, the caudate, hippocampus) and behavior control (i.e., lateral prefrontal cortex) [164–170]. Therefore, the mere presentation of food pictures, independent of gustatory activation, may be sufficient to evoke activity in the brain network implicated in eating behavior [98], although other factors should be also considered [171]. This may translate in the detrimental UPF-related nutritional aspects and features to be overridden by these visual cues related to the sensory and hedonic aspects of these products.

Environmental food cues also interact with the individuals' cognitive functioning and influence UPF intake. For instance, these cues may be more likely to encourage individuals to overeat if deficits in executive control are present [172]. In adolescents, Jensen and colleagues [173] showed that individuals highly motivated for the consumption of high-energy foods also demonstrated lower neural activation in inhibitory-related brain regions when viewing images of high-energy foods. Similarly, healthy young adults showed increased food-cue reactivity in the nucleus accumbens associated with snack food consumption and increased BMI, although this last association was only significant in those participants with low self-control [174]. In addition, it has been shown that the effects of UPF marketing on cognition may influence taste sensitivity. One explanation is that cognitive load (e.g., TVs) reduces taste perception, and thus people would tend to have more food to retain the same preferred taste levels and preserve food enjoyment as compared to relaxed food conditions [175, 176]. An alternative suggestion is that taste may be influenced by prior product information, or the expectations generated around the food product. The information provided in UPF packages is provided in a way that it overcomes the human limited capacity to process information; it is simple, concrete and imaging-provoking. This type of information engages people to find easy and rapid solutions (e.g., what to buy) based on the most relevant aspects of the problem (i.e., the salient information of UPF labels), instead on large amounts of information (e.g., the ingredients list) [177]. In this line, studies have found that taste responses in the insular and opercular gustatory cortices are modulated by expectations of a tastant [103] and word-level descriptors [178]. Finally, some research indicates that prior regular contact with UPF may increase the risk for excessive intake. For instance, regular *vs* non-regular Coke consumers showed less activation in an inhibitory-related ventral orbitofrontal region during anticipated Coke intake (i.e., the viewing of a bottle of Coke) [164].

5. Conclusions and future perspectives

Recent research has shed light on the adverse effects that UPF features have on health, beyond its nutritional composition that, for some UPF products, overlap with that from other foods highly consumed in Western diets. The UPF-related adverse health effects have the potential to impact on the neural network implicated in eating behavior, including the potential impact on serotonergic and dopaminergic neurotransmission, brain integrity and function. However, much work remains to be done in humans before being able to weight the specific impact of UPF intake on mental health.

The generalized intake of UPF make their potential negative consequences to seem harmless compared to other much studied factors, such as stress and drug exposures. However, it worth to remember that the highest UPF consumption coincide with plastic neurodevelopmental periods, such as childhood and adolescence [26]. At some ages, cognitive abilities may impact the ability of children to engage with food systems. For instance, younger children (< 5 years old) may not understand the persuasive intent of advertising (e.g., the selling of products) as they depart from one-dimensional judgement (e.g., like/dislike) and are unable to differentiate the information they receive for accuracy [27]. In adolescence, advertisement information should compete with peer pressures, looks, feels, the emotive messages of advertising, and tastes of foods, which may play a role into their developmental concerns related to appearance, self-identity, belonging, and sexuality [27]. At the same time, they may be less motivated by the long-term consequences of their diets [179] and greater tolerance for risks when consequences are ambiguous [180].

Learned taste preferences for UPF are of particular concern, as children get older because they can result in high intakes of these products, having adverse health consequences. Increasing the understanding of how UPF impact on highly automatic behaviors (e.g., oral processing and eating rate) during early childhood may help in designing strategies to prevent overconsumption and the development of obesity and associated conditions in future generations. However, direct effects of UPF consumption on brain development and the impact on eating behaviors at these ages remains to be explored. Finally, the easy accessibility to UPF may pose a significant problem for individuals with executive dysfunction such as inhibitory control deficits [172], showing a high motivational impact for these products when confronted with them in everyday lives.

To make the effects of UPF on mental health visible there is the need to provide compelling evidence of lifelong exposures (instead of short exposures) and objective metrics indicative of brain development (e.g., brain imaging techniques) and characterizing the mechanisms underlying these effects.

Declarations

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Figure and Table Legends

Fig1. Ultra-processed foods and drinks features and altered mechanisms. Ultra-processed foods and drinks are characterized by concrete features beyond their typically high-fat and sugary composition. These features comprise characteristic organoleptic properties (e.g., taste, texture), a high level of additives (including low-/non-calorie sweeteners –LNCSs–), trans-fats, and chemicals (e.g., bisphenols). Those have been associated with the alteration in several mechanisms, including those related to its oral processing, alterations in the gut microbiota, an uncoupling between the predicted calories from LNCSs and the consequent responses from the digestive system, inflammatory and oxidative stress processes.

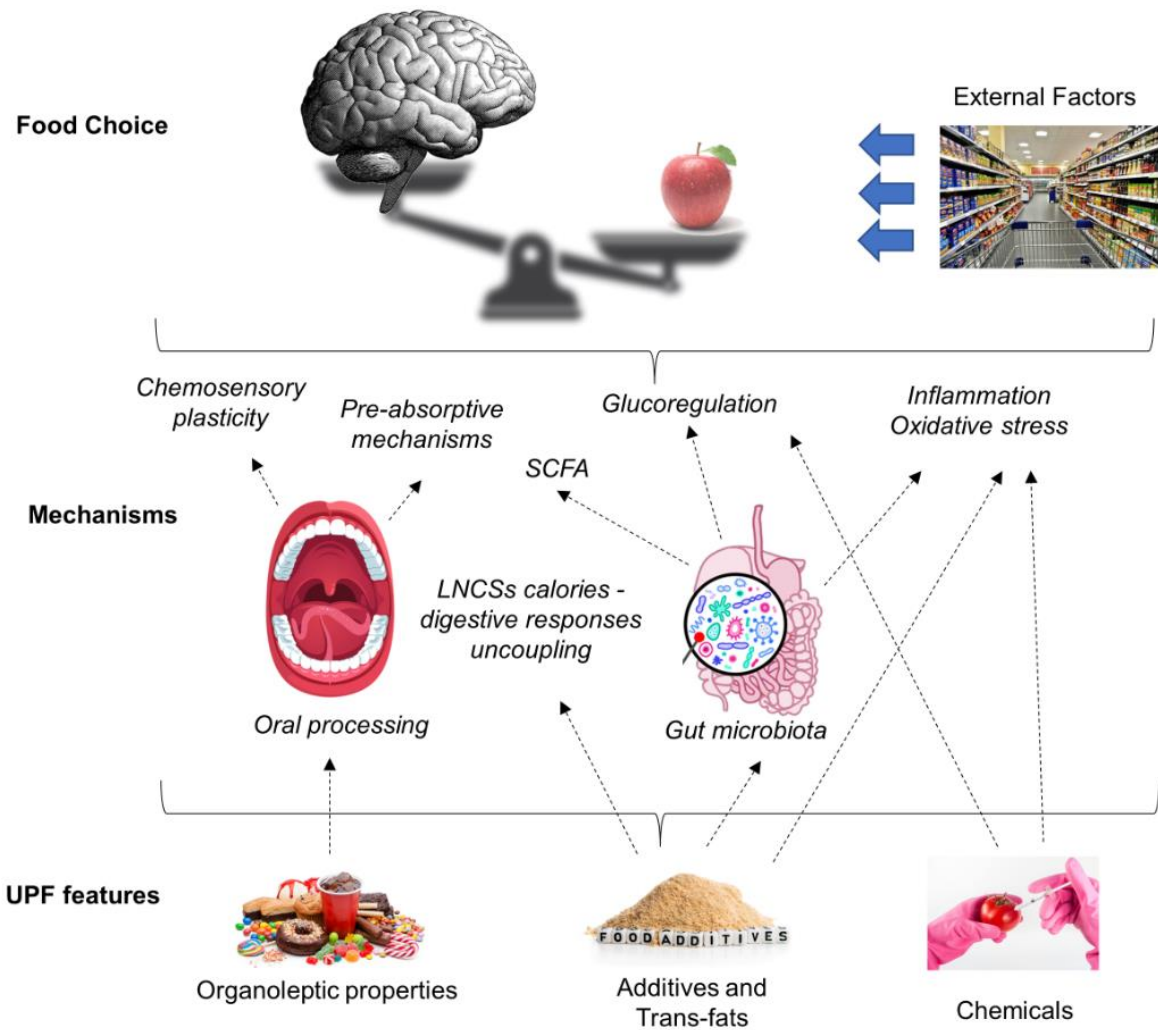


Fig2. Potential impact of ultra-processed foods and drinks features and associated altered mechanisms on the brain. The promotion of inflammatory processes associated with the consumption of ultra-processed products, and its content in nanoparticles and bisphenols may potentially affect serotonin (5-HT) and dopamine (DA) neurotransmission, and brain integrity. Brain integrity can be also challenged by trans-fats. Finally, the function in some brain regions implicated in eating behavior may be challenged by the consumption of low-/non-calorie sweeteners (LNCSs).

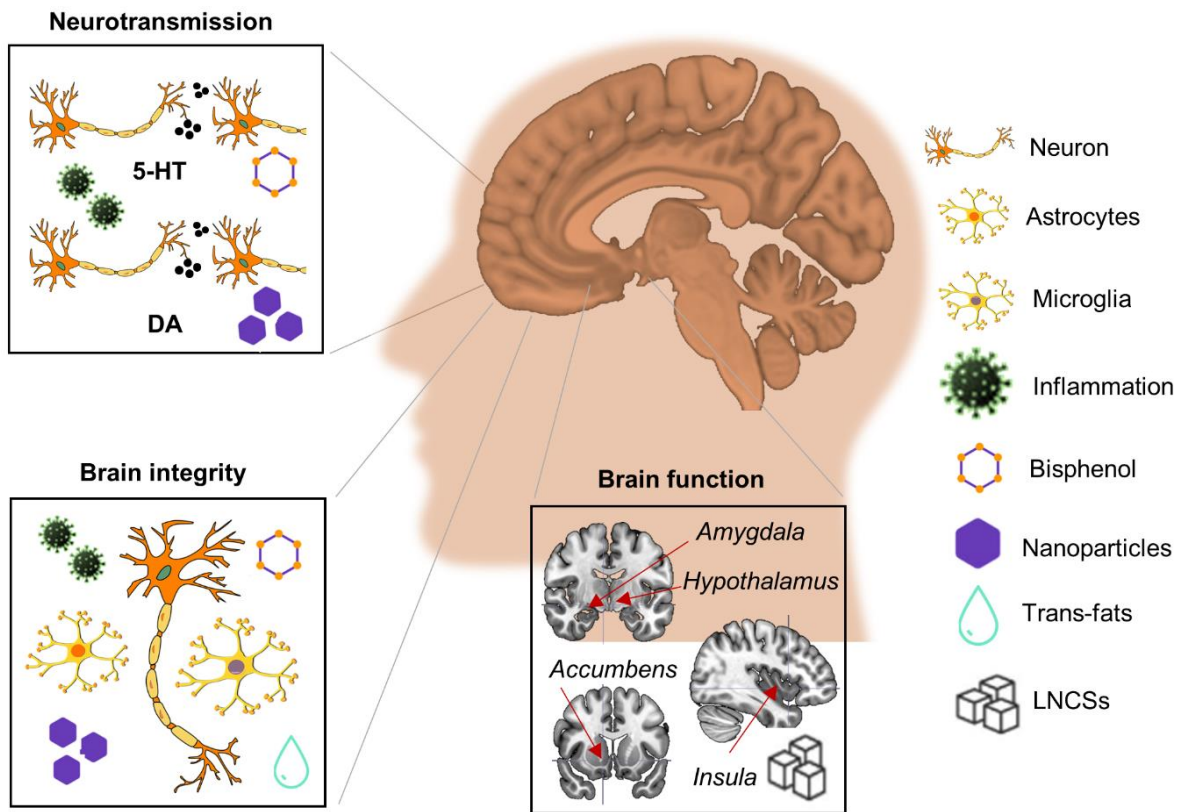


Table 1. Main studies that have recently synthesized the effects of food additives on gut health.

Table 1. Main studies that have recently synthesised the effects of food additives on gut health

Reference	Keywords	Contents	Type and number of studies included	Emulsifiers	UPF additives	Main conclusions related with the effects on gut microbiota
Bancal et al 2021	Emulsifiers; inflammation; colitis	Evidence linking emulsifiers to intestinal inflammation and human IBD. Pre-clinical studies in animal models and human clinical trials are reviewed.	In vitro studies (10), animal models including mice, rats, guinea pigs and rabbits (16 studies) and human dietary trials restricting emulsifiers (5 trials).		Polyorbate 60 (PB6), polyorbate-80 (PB8), carrageenan and carboxymethylcellulose (CMC)	Altered microbiota composition and behavior; ↑bacterial motility; ↑gut epithelium colonisation; SIBO; ↓bacterial adherence; ↑gut permeability; ↑mucosal thickness; ↓bacterial translocation; ↑LPS and flagellin; NF-κB and IκB-1D inflammatory pathways activation.
Cao et al 2020	Gut microbiota; food additives; artificial sweeteners; emulsifiers; preservatives	A summary and discussion of current findings on the impact of common food additives on gut microbiota structure and function. In vitro studies, animal models and human clinical trials are reviewed.	In vitro studies (9), animal models including mice, rats, rabbits and monkeys (21 studies) and human studies (1).	Non-Caloric Artificial Sweeteners	Acetamide potassium Aspartame Saccharin Sucralose Neotame Polyorbate 80 (PB80) Sorbitol Sodium benzoate, potassium sorbate, sodium nitrite and nitin Sodium benzoate Sodium citrate Titanium dioxide (E171) Organic acids (malic/ citric/ acetic acids)	Sex-dependent changes in fecal microbiota populations and -bacterial metabolites. Diet-dependent (chow vs high-fat) changes in fecal microbiota populations; ↑serum proinflammatory levels. In humans, changes in fecal bacterial diversity between consumers and non consumers. Different changes in the composition of gut microbiota across rodents' experiments; ↑expression of proinflammatory iNOS and TNF-α; ↓glycemic response. Different changes in the composition of gut microbiota across rodents' experiments; ↑ratio secondary/primary bile acid and ↓luminal levels of butyrate. ↓focal Firmicutes and ↑Bacteroidetes. Different changes in the fecal or jejunal/lumen composition of gut microbiota and LPS and flagellin levels across rodents' experiments. Differences in microbial diversity and changes in fecal populations. Bacteriostatic or bactericidal effects on different microbial communities. ↑mucosal permeability and changes in fecal populations. Specific changes in Firmicutes and Bacteroidetes. Different changes in gut microbiota composition and metabolites levels. ↑growth of pathogenic bacteria; ↑feces have bactericidal and bacteriostatic properties.
Laudis et al 2019	Western diet; microbiota diversity; IBD; colorectal; metformin; cells	Extensive systemic literature review (1995-2019). Pre-clinical studies and additives administered orally.	In vitro (5), rodents (21), pigs (1) and human (1) studies.	Emulsifiers Coating/Thickening Agents Non-Caloric Artificial Sweeteners	Carboxymethylcellulose (CMC) and polyorbate 80 (PB80) Mandelic acid (MDA) Saccharin, sucrose and aspartame Neotame Sorbitol Titanium dioxide (TiO2) E-Polylysine Silver nanoparticles (AgNPs) Triolein (TCS)	Dysbiosis; ↑intestinal inflammation; expansion of pro-inflammatory bacteria; sex specific behavioural and neural alterations. Expansion of adherent invasive E. coli strains; ↑mucus production; low grade intestine inflammation. Dysbiosis and altered microbial metabolites. ↑cholesterol and lipid secretion in faeces. Dysbiosis; ↑intestinal inflammation; Proteobacteria expansion; ↑lactin myeloperoxidase activity. Dysbiosis; ↑cytokine production; intestinal inflammation; ROS release; ↓gut permeability; alterations in gut immune system. ↑growth of the probiotic tax (Bifidobacterium and Lactobacillus); SCFA production; impairment of the intestinal epithelial barrier. Dysbiosis; intestinal microvilli and gland damage. Dysbiosis. Dysbiosis; low grade intestinal inflammation.
Medina-Reyes et al 2020	Engineered nanomaterials; food-grade nanoparticles; Western diets; food additives	Evidence of gastrotoxicity, hepatotoxicity and the impact of microbiota on gut-brain and gut-liver axis induced by colorants and anticaking additives, and their non-food grade nanosized counterparts after oral consumption.	Evidence from 32 in vitro, 35 in vivo rodent studies and 2 human studies, as well as 4 other reviews.	Colorants	Titanium dioxide (TiO2) Iron oxides and hydroxides Silver Gold Silicon dioxide (SiO2)	Food-grade (E171); intestinal inflammation. Non food-grade (TiO2 nanoparticles); intestinal oxidative stress; ↑proportion of harmful Actinobacteria and Proteobacteria and ↓beneficial Firmicutes and Bacteroidetes; intestinal inflammation; ↑richness and evenness of gut microbiota. No studies evaluating the microbiota alterations induced by iron oxide nanoparticles or E172 after oral exposure. Food-grade (E174); ↑ROS production in human colon cells. Non food grade (silver nanoparticles); disruption of the intestinal epithelium; ↑pro-inflammatory cytokines; ↑ROS production, mitochondrial dysfunction and apoptosis; ↓microbiome population density. Food-grade (E175); no studies evaluating the microbiota alteration. Non food grade (gold nanoparticles); gut dysbiosis by ↓Firmicutes/Bacteroidetes ratio and Lactobacillus and ↑Compositional dissimilarity. Food-grade (E551); alterations in intestinal permeability; intestinal pro-inflammatory response. Non-food grade (SiO2 nanoparticles); dysbiosis; Firmicutes and Proteobacteria and ↓Bacteroidetes and Lactobacillus population.
Nettelbladt et al 2016	Insulin resistance; low caloric sweetener; microbiota; glucoregulation; non-nutritive sweeteners	Evidence of regular long-term consumption of low-calorie sweeteners on the gut microbiota and insulin resistance, and the potential mechanisms.	Mainly rodent and human studies, also includes reviews and mini-reviews for discussion.	Low-calorie sweeteners	Sucralose, sucrose and aspartame	Glucose intolerance; altered microbiota composition and metabolite production (SCFA); endotoxaemia (↑LPS); ↑gut permeability; chronic inflammation.
Plaza-Date et al 2020	Non-nutritive sweeteners; sweetening agents; gut microbiota	An update about sweeteners' effects and their plausible biological interactions (i.e. a one component of a method of reasoning to establish cause-and-effect relationship) with the gut microbiota. Literature search from 2018 to 2020.	Apart from those studies referred to the ADME (absorption, distribution, metabolism and excretion) profiles, the specific effects of sweeteners on the intestinal microbiota are reviewed in 7 in vitro, 17 animal studies including mice, rats and dogs, 7 human studies and several reviews.	Non-Caloric Artificial Sweeteners	Aspartame-K Saccharin and sucralose Stevio glycosides Polyols	↑Firmicutes and ↓Bacteroidetes/ mucrophila populations. Changes in gut microbiota populations Might directly interact with the intestinal microbiota Probiotic properties with laxative effects

BD-10: Bifidobacterium longum; iNOS: inducible nitric oxide synthase; LPS: lipopolysaccharide; NF-κB: nuclear factor-κB; ROS: reactive oxygen species; SCFA: short-chain fatty acids; SIBO: small intestine bacterial overgrowth; TNF-α: tumor necrosis factor.