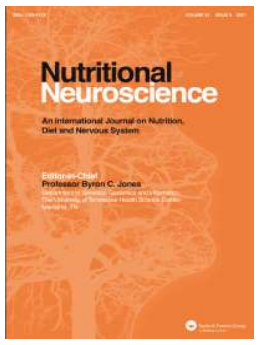

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Treating chronic stress and chronic pain by manipulating gut microbiota with diet: can we kill two birds with one stone?

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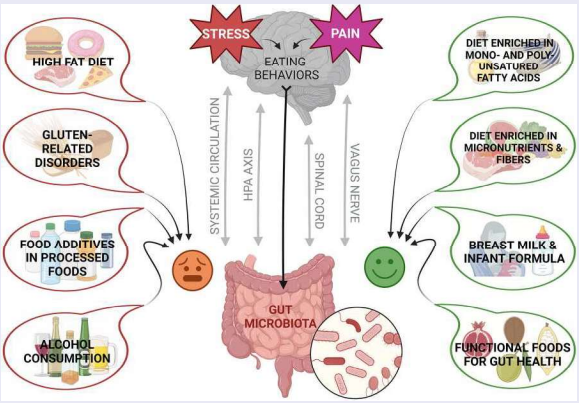
ABSTRACT

Background: Chronic stress and chronic pain are closely linked by the capacity to exacerbate each other, sharing common roots in the brain and in the gut. The strict intersection between these two neurological diseases makes important to have a therapeutic strategy aimed at preventing both to maintain mental health in patients. Diet is an modifiable lifestyle factor associated with gut-brain axis diseases and there is growing interest in its use as adjuvant to main therapies. Several evidence attest the impact of specific diets or nutrients on chronic stress-related disorders and pain with a good degree of certainty. A daily adequate intake of foods containing micronutrients such as amino acids, minerals and vitamins, as well as the reduction in the consumption of processed food products can have a positive impact on microbiota and gut health. Many nutrients are endowed of prebiotic, anti-inflammatory, immunomodulatory and neuroprotective potential which make them useful tools helping the management of chronic stress and pain in patients. Dietary regimes, as intermittent fasting or caloric restriction, are promising, although further studies are needed to optimize protocols according to patient's medical history, age and sex. Moreover, by supporting gut microbiota health with diet is possible to attenuate comorbidities such as obesity, gastrointestinal dysfunction and mood disorders, thus reducing healthcare costs related to chronic stress or pain.

Objective: This review summarize the most recent evidence on the microbiota-mediated beneficial effects of macro- and micronutrients, dietary-related factors, specific nutritional regimens and dietary intervention on these pathological conditions.



KEYWORDS

Microbiota health; dietary intervention; stress and pain management; gut-brain axis; gastrointestinal health; mental health; dysbiosis; nutritional therapy

Chronic stress and chronic pain as gut–brain disorders

Chronic pain and chronic stress still represent a clinical burden especially because the pharmacological therapies are limited by side effects and poor efficacy. These diseases share some pathophysiological factors, affecting common organ systems in the body and intertwined molecular mechanisms. Both chronic stress and chronic pain are related to the phenomenon of neuroplasticity in the central nervous system with a high incidence of psychiatric disorders, such as depression, anxiety and eating disorders [1,2]. Exposure to chronic stress can affect the pain threshold [3]; *vice versa*, chronic pain determines a condition of chronic stress, feeding a *vicious circle*

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that is responsible for a progressive lowering of patients' quality of life [4,5]. Additionally, both stress and pain have a significant impact on microbiota [6,7], which is involved in modulating brain processes, including stress responsiveness, pain modulation, ingestive behaviour, and brain biochemistry, throughout a variety of pathways (systemic blood and lymphatic circulation, vagal and spinothalamic afferences) [8]. On the other hand, the microbiota is a 'victim' of the brain, which exerts regulatory effects on gut physiology by the vagal and autonomic system as well as by the HPA signalling, causing common comorbidities of stress and pain, like visceral hypersensitivity, lower appetite and gastrointestinal motility disorders [9]. The interconnection between chronic pain and chronic stress disorders poses the base to identify an effective therapy able to manage both problems in one shot, by restoring a *virtuous circle* in the communication between brain and gut. Considering the high impact of nutrition on both microbiota and mental health, an interesting possibility is to use a dietary approach that is able to fuel microbiota, to counteract chronic pain and chronic stress effects on the body (Table 1).

Chronic stress, chronic pain and eating behaviour

Everyday life stressors, nutrition and dietary habits influence each other, independently or in concert impacting the body's homeostasis. Stress is recognized as risk factor for obesity and overeating [53,54] due to the chronic stimulation of hypothalamic–pituitary–adrenal (HPA) axis, which dramatically increases glucocorticoids, known to be orexigenic [55,56]. The increase in food intake can also be considered a coping mechanism to find relief from stress, shifting the nutritional demands to the emotional needs [57]. Anyway, prolonged exposure to stressful situations may also suppress appetite as a readout of the depressive and anxiety states often triggered by chronic stress [56,58]. Indeed, glucocorticoids can show anorexigenic effects, by the inhibition of AgRP-expressing cells, which, in turn, activates the melanocortin system, involved in the control of food intake and energy expenditure [59]. The effect of stress on eating patterns is influenced by gender [60] and by stress exposure during specific stages of life; a critical period is adolescence [61].

The connection between chronic pain and eating behaviour is also complex. Chronic pain is associated with anhedonia and decreased motivation, caused by neuroadaptations in the brain's limbic system [62] and in particular in the *nucleus accumbens* [63]. These alterations increase the risk of obesity in pain patients, which also impacts microbiota function [64,65]. A retrospective cohort study of paediatric patients with chronic pain confirmed that adolescents, especially those who experience gastrointestinal issues, anxiety, and greater functional disability, are likely to develop eating disorders [66]. Nociception allows organisms to adapt to menacing situations acutely and chronically often by suppressing competing needs. Therefore, pain can attenuate appetite as a

Table 1. Nutritional intervention studies on the gut microbiota composition under chronic stress and chronic pain conditions.

Alterations in chronic stress/chronic pain			Microbiota changes	
Taxonomy				
Phylum		Family/Genus	Improved by	Deteriorated by
Firmicutes	Increase in Decrease in	Enterococcus, Ruminococcus, Clostridium, Lactobacillus, Eubacterium, Roseburia, Faecalibacterium	Dietary fibers[1] (SCFAs) FOSs[2] Tryptophan[3] *N*-acylethanolmine[4] *n*−3 PUFAs[5] Vitamins[6] Breast milk[7] Folic acid[8] Functional food[9]	High fat diet[10] Alcohol[11] Food additives[12]
Bacteroidetes	Decrease in	Prevotella, Coprococcus, Suterella		
Actinobacteria	Decrease in	Bifidobacterium		
Proteobacteria	Increase in	Escherichia, Shigella		
Verrucomicrobia	Decrease in	Akkermansia		

[1][10–13]
[2][14–17]
[3][18–21]
[4][22–24]
[5][25–27]
[6][28,29]
[7][30–33]
[8][28]
[9][34–40]
[10][41–45]
[11][46,47]
[12][48–52]

means of prioritizing healing, and recovery, a phenomenon, which has been associated with the activation of specific neuronal pathways in the brain and the release of cytokines as part of the body's immune response [67,68]. In this context, it is important to consider that either physical inactivity, eating disorders or sleep disturbance related to chronic pain impact gut microbiota [69–72]. It is thus clear that the relationship between eating, stress and pain is complex and might be influenced by several factors related to the personal history of each patient. Therefore, if the intent is to use diet as a therapy, the first step is to understand the patient's eating behaviour and eventually re-educate it.

Dietary factors impacting positively or negatively on pain and stress: microbiota implication

The microbes in the gut respond to dietary intervention and play an important role in energy extraction from food as well as the biotransformation of nutrients [73]. The identification of dietary components that might be metabolized by members of gut bacteria into active products able to mediate beneficial microbe–microbe and microbe–host interactions might represent a new approach for modulating host biology in order to obtain benefits on chronic stress and pain. In gastrointestinal disorders characterized by chronic abdominal pain, such as IBS, the diet has been regarded as a first-line treatment, and the removal of the most 'harmful foods' from the diet is a common medical practise [74]. Diet therapies can reduce abdominal pain through multiple mechanisms, including changes in the microbiota composition and metabolite output [75]. Although diet is not considered a first-line treatment in chronic stress therapy, nutrition has recently been appraised as an adjuvant treatment [76–78]. However, the relatively few studies, compared to those on the diet effect on chronic pain, showed the successful alleviation of stress-related symptomatology by dietary intervention. Some of the diet effects on mood and management of stress symptoms are linked to gut microbiome changes. In a multidirectional interaction, diet can affect the microbiome, which, in turn, affects brain health. In the next paragraphs, we will discuss the last evidence about the potential effects of dietary components on gut–brain axis physiology and their possible impact on chronic stress and chronic pain pathology and therapy.

Macro- and micronutrients

Amino acids

Tryptophan is an essential amino acid that can be metabolized by different pathways to serotonin (5-HT) or to kynurenine (KYN) and in turn to kynurenic acid (KA) and quinolinic acid (QA). 5-HT shows a double face in pain modulation: in the periphery serotonergic activation of DRG, neurons innervating the viscera and the skin mediate nociceptive transmission [79], while descending serotonergic pathways can inhibit or facilitate pain transmission at the spinal level [80]. In the 5-HT pathway, TRP is converted to serotonin, while, in gut microbes, tryptophan is metabolized into indole and indole derivatives [81]. Although colonic luminal aromatic amines, such as TRP, have been historically considered to derive from foods, recent studies indicate that gut microbiota, in particular five prominent genera of Firmicutes (*Blautia, Clostridium, Enterococcus, Ruminococcus,* and *Tyzzerella*), can serve as an alternative source of these amines [18]. Hence, gut microbiota is crucially involved in TRP metabolism [82,83]. TRP and its metabolites, especially serotonin, are long-standing known to be implicated in the pathogenesis of stress-related disorders such as anxiety and depression for which medications promoting central 5-HT availability are the standard therapy. There are reports on both the beneficial effects of TRP supplementation and the dysregulation of TRP metabolism in chronic stress conditions [19,20], in which the KYN pathway is more favoured than the 5-HT pathway [21,84,85]. In this condition, a TRP-rich diet improves neuroinflammation, expression of BDNF, and mitochondrial energy metabolism and reconstructs gut microbiome, increasing the relative abundance of *Lachnospiracea*, *Clostridium*, *Lactobacillus*, *Bifidobacterium* [21]. Accordingly, prebiotics from the genus *Bifidobacterium* can reduce inflammation by increasing TRP availability [86].

Another important essential amino acid present in animal and plant protein is L-histidine, the precursor of histamine. Histamine is peripherally released by mast cells and found to be involved in both inflammatory and neuropathic pain [87–92]. Interestingly, a crosstalk between mast cells and glia has been recently proposed as a mechanism regulating opioid tolerance and therefore pain physiology [93,94]. Even though this relationship was not confirmed in the gut, both mast cells and enteric glia have an important role in the regulation of gastrointestinal pain [95,96], and it

is interesting to note that their functions are directly influenced by the resident microbiota [17,97]. Yet, researchers from McMaster University and Queen's University identified a gut bacterial 'super-producer' of histamine, *Klebsiella aerogenes,* that can cause pain flare-ups in some patients with IBS. The bacterial histamine can activate the gut immune system through the histamine-4 receptor, which draws immune mast cells into the intestines, where they produce even more histamine and other pain-signalling mediators, triggering inflammation and pain [17].

The histaminergic system was recently reported to play a role also in chronic stress-induced dysfunctions [25,98]. Several evidence suggest that histaminergic neurons detect stress-induced signals [99]. Strictly related is also the dependence of histaminergic receptor expression in different rat brain areas during prolonged stress exposure [100]. Accordingly, histamine-depleted mice are insensitive towards the effects of a protective agent against stress-induced disorders [101], demonstrating the crucial role of brain histamine in the management of stress. Dietary supplementation with histidine and *Lactobacillus reuteri* was shown to increase histidine decarboxylase expression and consequently histamine synthesis, an effect that inhibited also the production of TNF-α in myeloid progenitor cells [102]. The fact that l-histidine is an essential amino acid that can be introduced with the diet and that it can be metabolized by the gut resident bacteria to histamine opens the possibility of using the microbiota to modulate histaminergic signalling through the gut–brain axis, obtaining benefits in certain chronic pain conditions.

Lipids

Several bioactive lipids, such as N-arachidonoylethanolamine (AEA), palmitoylethanolamide (PEA), oleoilethanolamide (OEA), bile acids, and SCFAs, are able to modulate peripheral and central pathologic processes. A possible correlation between these lipids and gut microbiota through different mechanisms has recently been reviewed [103]. In a mouse model of IBS caused by early-life stress, the decreased abundance of *Ligilactobacillus murinus* was associated with both visceral hypersensitivity and deficits in the production of GABA-containing lipopeptides, whose concentration is decreased in faeces from IBS patients [104]. Another work highlighted the immunomodulatory properties of α-galactosylceramides from the human symbiont *Bacteroides fragilis* [105]. Although the role of these lipids has not been investigated in the context of pain, a close link between immune response derangement and chronic pain physiology has been proposed [106]. Therefore, we cannot exclude in the future the possibility of counteracting chronic pain by pushing the metabolism of gut microbiota towards products able to redirect the altered immune response.

Between biogenic lipids, PEA and OEA are considered a paracannabinoid system. PEA is also present in food, and it is initially extracted from soybean lecithin, egg yolk, and peanut meal [107], while OEA mobilization in the mucosa of the proximal intestine is controlled by nutrient availability [108]. OEA administration in mice is capable of modulating gut microbiota composition, reducing the abundance of *Lactobacillus reuteri* and *Lactobacillus gasseri* and increasing those of *Bacteroides acidifaciens,* shifting gut microbiota towards a 'lean-like phenotype' [22,23]. Also, PEA can counteract dysbiosis by increasing the abundance of *Akkermansia muciniphila,* Eubacterium and Enterobacteriaceae [24]. The actions of PEA and OEA, on gut microbiome homeostasis, could explain some of their central and peripheral effects. Indeed, gut microbes are involved in the development and function of the HPA axis, which coordinates the adaptive stress response in the body [109], which is dysregulated in anxiety and depressive disorders [110], typically associated with chronic stress conditions. Depression has been associated with a lower abundance of Bacteroidetes (*Prevotellaceae, Faecalibacterium, Coprococcus,* and *Sutterella*) as well as a higher abundance of *Actinobacteria* and *Eggerthella* [111]. OEA's ability to augment the Firmicutes:Bacterioidetes ratio could improve depression related to stress.

Indeed, we recently demonstrated the OEA protective role against psychosocial stress-induced dysfunctions, an effect that required the integrity of the histaminergic system [101]. Both OEA and PEA's beneficial effects against chronic stress-induced behavioural and neurochemical alterations were proven in models of CUMS [112,113]. According to preclinical evidence, in a Trier Social Stress Test, a clinical study on depressed women, lower serum PEA and OEA concentrations relative to baseline was found [114], demonstrating an important correlation between stress and acylethanolamines.

Both OEA and PEA are known as an effective and well-tolerated adjuvant treatment for pain, and they find clinical application in the management of several chronic diseases, such as in the treatment of peripheral neuropathic pain, inflammatory, musculoskeletal pain and in palliative care [107,115], by acting on nuclear peroxisome proliferator-activated receptors (PPARs)

[116–121], transient receptor potential vanilloid type-1 [122–124], GPR55 and GPR119 [122,124]. Moreover, PEA delays the onset of tolerance to morphine's anti-nociceptive effects, raising the possibility of using this nutrient for improving opioid-based therapies [93,125–127]. PEA can also inhibit mast cell activation [93,94,128] and prevent enteric glial hyperactivation [129], two phenomena involved in visceral pain [130,131] and therefore two potential therapeutic targets [132,133]. Intriguingly, PEA counteracts gut inflammation and prevents dysbiosis by increasing the level of commensal bacteria such as *Akkermansia muciniphila, Eubacterium and Enterobacteriaceae* [24]. OEA is also involved in the maintenance of microbiota–gut–brain axis physiology through the modulation of vagus nerve activity [134], which inhibits inflammation, oxidative stress, and sympathetic activity and activates brain regions that can oppose pain-signalling in the brain [135]. For these reasons, PEA and OEA are becoming a promising topic in microbiome research.

The gut microbiome is a crucial player also in bile acids metabolism. The interactions between the gut microbiome and these lipids are bidirectional, whereby bile acids affect the composition of the gut microbiome, and the latter regulates the composition and size of the bile acids pool [136,137]. Of particular interest, gut microbiome–associated bile acid alterations have been suggested as a putative mechanism in the development of visceral pain in IBS [138,139]. High consumption of fat (i.e. Westernized diets) stimulates hepatic synthesis of bile acids, resulting in increased amounts of bile acids that escape ileal reabsorption and enter the colon, where they undergo biotransformation by gut bacteria [140]. Therefore, a modification of the type and the amount of lipids introduced with diet, or modulation of microbiota metabolism, might be used as a strategy to adjuvant pain pharmacotherapy in certain pathological conditions.

In the context of lipids as nutrients to treat chronic stress and chronic pain, worth mentioning are the Omega-3 polyunsaturated fatty acids (n-3 PUFAs), such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and α-linolenic acid (ALA) [141]. Several preclinical and clinical data showed that dietary n-3 PUFA intake can prevent changes in different domains altered by stress exposure [142]. In this regard, we recently demonstrated the role of the histaminergic system in the beneficial effects of an n-3 PUFA + VitA enriched diet in preventing the deleterious effects of psychosocial stress in mice [25]. Moreover, dietary enrichment in case of histamine depletion changed the gut microbiome profile in terms of tryptophan and histidine degradation [25]. In addition, a restorative effect of n-3 PUFA + VitA on a multitude of taxa altered by stress during adolescence, such as *Lachnospiraceae* and *Ruminococcaceae* (decreased in patients with depression [143] and *Coriobacteriaceae*) associated with gut health [144] was reported [26]. Preclinical and clinical studies evaluating the gut microbiota composition under diverse timing and type of n-3 PUFAs supplementation concorded on similar modifications: a decrease in *Faecalibacterium*, an increase in the Lachnospiraceae family, genus *Roseburia*, and Bacteroidetes [27].

A recent clinical trial attested that increased n-3 PUFA intake was inversely associated with pain incidence and worsening [145]. This finding has been preceded by preclinical studies demonstrating the beneficial effects of supplementation of n-3 PUFAs in models of inflammatory and neuropathic pain originating from different organs [146–152]. Although a clear demonstration has not been provided yet, the aforementioned modulation of gut microbiota by n-3 PUFAs might contribute to their effects on both pain and stress-related disorders.

Vitamins

Vitamins are micronutrients required by the body to carry out a range of normal functions [153]. Vitamin D (VitD) deficiency is highly prevalent worldwide and has been suggested to be associated with an increased risk of emotional disorders [154] as well as with changes in epithelial barrier functions and microbiome setting in patients, including those with IBS [155–158]. VitD-deficient mice showed a reduced microbial diversity associated with tactile allodynia, neuronal hyperexcitability and alterations of endocannabinoid system members at both gut and spinal cord levels [24]. Other evidence supported an inverse correlation between VitD levels and painful manifestations [159,160]. Few foods naturally contain VitD (i.e. the flesh of fatty fish and fish liver oils), but foods fortified with VitD, like dairy products and cereals, are available [153,161]. The therapeutic value of VitD supplementation was investigated in rat models of CUMS [162–165]. These studies revealed that VitD improves chronic stress-induced dysfunction in part via decreasing brain oxidative stress and inhibiting neuroinflammation. Gut microbiota, in particular the abundance of certain bacteria (*Akkermansia* and *Bifidobacterium*), might represent a mechanism yet unexplored for these beneficial effects [166,167].

Folate, the natural form of the water-soluble vitamin B9 (VitB), is also present in foods. Notably, the concentration of folate was found to be markedly decreased in the peripheral blood of IBS patients compared with non-IBS human subjects. Folate supplement alleviated chronic visceral pain and reduced the spontaneous activity of neurons in the spinal dorsal horn of rats undergoing neonatal colonic inflammation, which was associated with a significant reduction of H_2S production by *Clostridiales* [28]. A direct link between VitB and chronic stress was not investigated, as the best of our knowledge. Anyway, when under stress, the body uses VitB reserve to assist metabolic processes for energy production [168]. Moreover, colonic metabolites, such as VitB, were reported to be responsive to psychosocial stress. In mice, prebiotics attenuated the effects of social stressors by increasing colonic VitB levels, suggesting an expansion of gut microbes capable of producing VitB, including *Bifidobacterium* [29].

Beta-carotene is a pigment found in plants and food that gives them their yellow and orange colour with antioxidant activity [169]. Recently emerged that the combination of Beta-carotene and green tea was able to regulate serum uric acid levels by affecting the gut microbiota, thereby improving the symptoms of gout, such as persistent pain [170]. Gout is a painful disease caused by disorders of purine metabolism [171], which is finely regulated by gut microbiota [172]. Purine-derived adenosine and ATP have an important role in pain physiology [173]. Intriguingly, alterations in purine metabolism have been associated with painful symptomatology in patients affected by irritable bowel syndrome [174].

Dietary-related factors

High-fat diet (HFD)

Chronic HFD consumption is known to induce changes in physiology and behaviour similar to that caused by chronic stress [175,176]. In particular, prolonged HFD intake induces dysbiosis of gut microbiota and impairs intestinal barrier integrity, subsequently inducing neurobehavioral disorders through systemic and neuronal inflammation [177]. Analogously, stress affects the function of the GI system modifying, among others, the permeability of the intestinal barrier, increasing inflammation, etc. [178], which has an impact on behaviour.

However, whether chronic stress exacerbates HFD-induced changes and vice versa, it stills a matter of debate. Preclinical studies suggest from one side a deleterious effect of HFD and stress combination [179,180]. On the other side, the protective effects of HFD on stress-induced alterations were proposed [181–183]. Further studies are needed to disentangle the relationship between HFD and chronic stress [182], both having a strong impact on gut microbiota.

Even if the Firmicutes/Bacteroidetes ratio is just simplistically considered a taxonomic signature of obesity, being this parameter highly variable between different studies and conditions associated with obesity [184], an unbalanced proportion of Bacteroidetes versus Firmicutes with a reduction of the formers (i.e. *Bifidobacterium*, *Tenericutes*, *Bacteroides*, *Lactobacillus* and *Roseburia*) and an increase of the latters (i.e. Firmicutes, Actinobacteria, and Proteobacteria) was reported by several studies evaluating the microbiota composition under HFD conditions in rodents [42] as well as in obese humans [43–45]. A similar reduction in the relative abundance of bacteria in the genus Bacteroides has been associated with stressor exposure [41]. Therefore, it can be assumed that HFD- and chronic stress-related disorders can benefit each other from a nutritional intervention aimed at correcting the common modifications in the microbiome. In this context, sexual dimorphism has to be taken into account. Although the HFD and chronic stress exposures independently or in combination shift the microbiota composition in male and female mice, stress in female mice seems to cause shifts in the gut microbiota similar to those observed in HFD-fed mice. An effect that was not reported in male mice, suggesting a gender dependence of gut microbiota composition in response to HFD and chronic stress [185].

Obesity has been associated with increased susceptibility to chronic pain, though the linking mechanisms are still unclear [186]. A 45% HFD was correlated with visceral pain, fibromyalgia-like pain, pelvic pain, inflammatory hyperalgesia, and neuropathic pain, while a 60% HFD has been reported to worsen postoperative pain, trigger muscle pain during walking and contribute to chronic pain condition and neuropathic pain [187]. Even if a correlation does not always imply causation, dietary weight loss in people with severe obesity can stabilize neuropathy (intraepidermal nerve fibres loss) [188,189]. By using germ free mice, it has been observed that HFD-induced gut microbial changes can also contribute to the development of enteric neuropathy [190]. The intestinal microbiome might provide a potential link between dietary fat intake and nerve health. Intriguingly,

specific gut microbial taxa correlating positively with metabolic health were inversely associated with peripheral neuropathy in HFD-fed mice, while specific taxa negatively linked to metabolic health were positively associated with this painful neurological disorder. Neuropathy-associated taxa variants, including *Lactobacillus*, *Lachnoclostridium*, and *Anaerotruncus*, were also positively correlated with several lipid species, especially elevated plasma sphingomyelins and sciatic nerve triglycerides, while negative correlations were additionally found with other taxa variants [191]. Based on this evidence, it can be supposed that HFD is able to regulate chronic pain via gut microbial effects.

Alcohol

In addition to being a risk factor for the development of chronic pain [30,192,193], individuals undergoing acute alcohol withdrawal exhibit greater pain sensitivity [194–196], which, in turn, can lead to relapse in recovering from alcoholism. Gut microbial diversity is markedly affected by alcohol consumption [197–199] and recent evidence attested that alcohol-induced mechanical hyperalgesia was markedly attenuated in rats receiving probiotics [200]. Alcohol-induced gut dysbiosis was associated with decreased abundance of *Clostridia, Bacilli* and *Bacteroidetes,* and an increased percentage of *Gammaproteobacteria* and decrease in species like *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* have also been reported [46,47]. In addition, chronic alcohol consumption disrupts epithelial barrier, thereby increasing gut permeability to microbes and bacterial products [200]. Mechanistically, alcohol consumption is associated with the upregulation of important neurotransmitters namely dopamine, GABA, Serotonin and norepinephrine [201], which are produced by several important species of bacteria [202]. Although the direct effect of alcohol on the production of neurotransmitters or any other metabolite by the gut microbiome remains to be studied, it is conceivable to conclude that alcohol abuse impact on the gut–brain axis, resulting in adverse effects on the behaviour and also on the stress responses. Collectively, the data reported in the literature suggest that stress and alcohol consumption affect each other. Alcohol is long-standing known for its ability to alleviate stress [203–205]. Importantly, chronic stress exposure during adolescence can produce an increased propensity to self-administer alcohol later in adulthood [203,206].

Food additives

The Westernization of eating habits has led to the increasing consumption of food additives incorporated in almost all processed food, which can directly impact microbiota–gut–brain axis [207]. Some studies have demonstrated that the consumption of artificial sweeteners determines an overgrowth of *Bacteroides, Lactobacillaceae* and *Enterobacteriaceae* [48–50], which were found to be increased also in IBS patients [208]. Anyway, every cloud has a silver lining. Among naturally occurring sugars there are polyols, like lactitol, whose consumption was found to positively influence the gut microbiota's composition, i.e. by enhancing the growth of *Akkermansia* [209], whose abundance was negatively associated with neuropathic and abdominal pain conditions [24,210]. Yet, mice fed high fructose corn syrup-moderate fat diet displayed enhanced anxiogenesis, increased behavioural despair, and impaired social interactions, an effect associated with gut dysbiosis [51]. Fructose consumption can impair serotonergic signalling in mice's enteric nervous system [211]. It remains to understand if the dysregulation of gut–brain signalling caused by fructose consumption might be associated with an increased risk of developing chronic hyperalgesia. The same goes for the emulsifiers [212–215] and for food colourants [216,217] as various studies attested to their capacity directly alter microbiota composition, resembling post-infectious IBS [52]. Yet, food preservatives are natural or synthetic additives that delay degradation by inhibiting the growth of bacteria and fungi, but little is known about their effect on microbiota [218,219]. Looking at other additives, a recent study has shown that the administration of aluminium in rodents, at doses relevant for human consumption, can trigger visceral hypersensitivity through the protease-activated receptor-2-mediated activation of mast cells and the subsequent release of tryptase and histamine [220]. Future studies are thus essential to further evaluate the impact of food additives gut–brain axis and their implications in chronic pain and chronic stress-related disorders.

Functional foods

Many foods naturally contain prebiotics, compounds that support the growth and/or the activity of beneficial microorganisms within the gut. Melanoidins are products of the Maillard reaction between carbonyl and amino groups of macromolecules readily formed in foods during heat treatment. They can trap cations that are essential for the growth and

survival of pathogenic bacteria [34,221]. Furthermore, melanoidins can be used as carbon and nitrogen sources by the hindgut bacteria, supporting the growth *Bifidobacteria and Faecalibateria* [34–36]. Considering their relevance in our diet (average amounts of 10 g/day), melanoidins might represent an interesting and unexplored field of research in the area of chronic disorders like stress and pain. There are also several common foods that can act on either the gut microbiota or the nervous system, for example, pomegranate [37], which has been largely investigated for the management of pain [222–224]. Ellagitannins, together with polyphenols and polysaccharides, derived from pomegranate were found to be responsible for the protective effect of pomegranate extract against chronic pain and chronic stress [225–227]. Noteworthy, multiple biological activities of ellagitannins are closely linked to the gut microbiota, which enhances their systemic bioavailability and efficacy by the transformation into bioactive urolithins [228].

There are a host of foods well-studied for their role in pain management, like extra virgin olive oil (EVOO) [229], coffee [230–232] and chocolate [233], primarily because of their anti-inflammatory properties. Recently, data are emerging, which demonstrate that the health-promoting benefits of these foods may also extend to the gut microbiota [38–40]. Nevertheless, there is still a lack of *in vivo* studies to validate such findings [234]. It is also important to mention the effect of food constituents (i.e. coffee) on gut motility, which might help in regularizing gastrointestinal transit, avoiding the risk of developing painful conditions like chronic constipation [235]. Although there are missing or scarce data, all of this food may prove useful as adjuvant therapy for the treatment of stress-related disorders since inflammation, oxidative stress and gut dysbiosis were reported in previous paragraphs as determinant in the progress of chronic stress.

Specific nutritional regimens

Gluten-free diet

In some individuals, gluten sensitivity was shown to manifest with neurological dysfunction, such as neuropathy and cerebellar ataxia [236]. In these patients, a strict gluten-free diet significantly reduced the odds of pain [237]. Another study reported that painful symptoms of endometriosis decrease after 12 months of gluten-free diet [238]. The rationale behind this is that gluten could increase proinflammatory cytokines production exacerbating chronic pelvic pain [239]. Gluten-related conditions are also associated with metabolic osteopathy and osteoarticular pain [240,241]. There are studies that proved that gluten consumption is responsible for both gastrointestinal symptoms such as recurrent abdominal pain, bloating, altered stool consistency, and non-gastrointestinal symptoms like tiredness, depression, and anxiety in patients with IBS [242]. However, this evidence was questioned due to the paucity of randomized, placebo-controlled trials [243]. Inflammation caused by gluten-related disorders could induce psychological effects including stress, anxiety and depression. In fact, a long-term gluten-free diet significantly reduced and normalized the severity of depressive symptoms for subjects suffering from coeliac disease, IBS and non-coeliac gluten sensitivity [244]. On the other hand, the gluten-free diet adherence and the hypervigilance to cross-contaminations were associated with a stressful condition [244,245]. Therefore, a balance between dietary adherence and well-being in the management of certain patients must be taken into account. Intriguingly, reactivity to gluten is also affected by gut microbiota, as several recent studies demonstrated that different bacteria metabolize gluten partially (e.g. *Lactobacillus*) or completely (e.g. *Prevotella*, *Veillonella*, *Staphylococcus*, and *Bacillus*) affecting the immunogenicity of gluten-derived peptides [246–248].

Breast milk

In the years, numerous benefits of breastfeeding over infant formula were established, partly due to the presence of human milk oligosaccharides (HMOs), a family of over 100 non–digestible carbohydrates resembling mucosal glycans that shape infant's microbiota [249]. HMO utilization is restricted to specific microbial taxa such as members of the *Bifidobacteriaceae*, *Bacteroidaceae* families and *Lachnospiraceae* [30–32]. Unlike FODMAP, HMOs are not digested by the intestinal microbiota [250,251], so they reach the large intestine where they can directly interact with the microbiota or be absorbed [32,252]. Feeding with sialylated HMOs reduced anxiety-like behaviour in mice submitted to chronic stress, likely via modulation of the gut microbiota composition and/or metabolism [253]. HMOs modulate the activity of GPR35, a receptor mediating attenuation of pain and colitis, also by upregulating the production of the GPR35 agonist kynurenic acid by the microbiota [254]. Yet, a recent work highlighted the capacity of HMOs to alleviate visceral hypersensitivity and associated microbiota dysbiosis in mice undergoing water

avoidance stress [33]. Unfortunately, the efficacy of HMO in patients with IBS is still controverse [255,256]. Other constituents of human breast milk exert positive effects on gut–brain axis, and these are the milk fat globule membrane (MFGM), a complex system of proteins, enzymes and lipids, derived from the mammary epithelium and secreted during lactation [257,258]. It has been observed that intervention with MFGM and prebiotics significantly impacted microbiota composition ameliorating some of the long-term effects of early-life stress in rats, such as visceral hypersensitivity and behavioural alterations. The combination also facilitated the return to baseline with regard to the HPA axis response to the restraint stress, reducing the long-term impact of maternal separation on prefrontal cortex neuroplasticity [259]. The large number of breast milk constituents together with the large number of microbial metabolites in the gut ecosystem constitutes a poorly explored library of natural compounds with a large potential to impact many physiological functions.

Dietary interventions

Dietary fibres and FODMAP

Beneficial health outcomes of dietary fibre have been mainly linked to the fibre-derived short-chain fatty acids (SCFAs) produced by microbial metabolism [260]. SCFAs are able to modulate pain by regulating the production of cytokines/chemokines, intestinal inflammation and epithelial barrier function [13]. They also directly impact the central nervous system by modulating energy metabolism, neuroinflammation, and blood–brain barrier permeability via their receptors FFAR2/3 and histone deacetylases [261–264]. The role of SCFAs in visceral and somatic pain perception is still subject of debate: depending on the context; the effect of SCFAs can be either analgesic or nociceptive [265–268]. Microbial-derived SCFAs can sensitize nociceptive neurones and may contribute to the pathogenesis of post-inflammatory visceral pain in mice [269]. Accordingly, Lucarini et al. observed that increased levels of SCFAs, in particular acetate, and the respective producing families of bacteria (es. *Lachnospiraceae*) in the gut lumen are associated with visceral hypersensitive caused by faecal microbiota transplantation [210]. SCFAs seem to also play a role in the pathogenesis of neuropathic pain by regulating microglial activation [270]. In this context, it might be important to consider even the sex of the patient as, in comparison with men, women displayed overall stronger associations between SCFAs and pain threshold [271].

Other than the sex of patients, an important factor to be taken into account when the role of SCFAs on pain modulation is studied is age. An interesting study recently showed an association between somatic complains (frequently referred by the young patients as GI disturbances or pain) and the gut microbiota and SCFAs in pre-school children [272]. The authors showed a reduced microbial alpha-diversity and SCFAs acetate and butyrate in faecal samples from pre-school children, which are both associated with somatic complains. An increased abundance of Lachnospiraceae unclassified, Tyzzerella4, Collinsella, Eggerthella, and Veillonella correlated with the internalizing behaviour score in somatic complains 'at risk' children and importantly such alterations were not reported in adult depressed patients as the authors suggested due to the fact that in children (specifically between 3 and 5 years of age), the gut microbiota is still developing suggesting an age-dependency of gut microbiota–mental health associations [272]. Therefore, in such situation, increasing endogenous SCFAs in pre-school children might reduce somatic complains [272].

Recent evidence highlighted a regulatory effect exerted by gut microbiome-derived SCFAs on the levels of neurotransmitters (norepinephrine, 5-HIAA and 5-HT) in the hypothalamus during chronic stress conditions in mice. In stressed animals, the authors found a decreased abundance of genus *Akkermansia* again positively correlated with 5-HT in the hypothalamus. A positive correlation also emerged between SCFAs and differential bacteria (*Alphaproteobacteria, Streptococcaceae, Staphylococcaceae*, *Spirochaetaceae)* [10]. In a model of CUMS, positive correlations between *Prevotellaceae*/propionic acid and *Ruminococcus bromii*/butyric acid as well as negative correlations between *Muribaculaceae*/butyric acid and *Bacteroidaceae*/propionic acid were found [11]. Thus, SCFAs supplementation could prevent the deleterious effect of chronic stress. The theory was indeed proved by another study demonstrating that SCFAs supplementation alleviates chronic psychosocial stress-related disorders, including gastrointestinal barrier dysfunctions [12].

Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) are poorly absorbed short-chain carbohydrates, which are rapidly fermented, resulting in osmotic overload, dysbiosis [273] and excessive gas production (like H_2 and H_2S), resulting in symptoms, like

bloating and cramping. Some individuals have a higher tolerance for of gas in their intestines. Others, like IBS patients, are unable to manage gas balance, manifesting digestive symptoms and persistent pain. Moreover, interactions between these dietary components and histamine producing bacteria play a key role in chronic abdominal pain in a subset of IBS patients [16,17], who can benefit from reducing dietary fermentable carbohydrates [274]. The same anti-hyperalgesic efficacy was not reached in patients with quiescent IBD [275]. Similar to IBS patients, stressed animals partially benefit from inulin enrichment [276]. Fructo-oligosaccharides (FOSs) intake can revert behavioural impairments induced by psychosocial stress in aged mice while it is not sufficient to counteract the increased inflammation induced by stress [14]. Some prebiotics-related changes in the bacterial taxa are also dependent from the age [277] and the administration time. The microbe distribution trend in stressed mice is affected by evening inulin treatment with a reduction in *Firmicutes* and increase in *Actinobacteria*. Both morning and evening inulin increases the abundance of *Enterococcaceae*, while only morning inulin increased the Lactobacillus, unclassified_f_*Lachnospiraceae*, and norank_f_Lachnospiraceae in stressed mice and decrease the *Ileibacterium* and *Dubosiella* which are significantly associated with inflammatory factors [15].

A complication of low FODMAP diets is that, frequently 'bad' and 'good' fibres are contained in the same foods. Furthermore, the deficiency in certain nutrient intakes may be confounders in interpreting the effects of a low FODMAP diet in clinical trials [278,279]. Most of the dietary fibres are considered prebiotics: inulin (onion, garlic and wheat), pectin (citrus fruits, peaches and roots), resistant starch (green bananas, oats and potatoes), and guar gum (thickening/stabilising agent). The related reduction in *Bifidobacteria* and *F. prausnitzii* during low FODMAP diet are of potential concern, as these bacteria have positive immune-regulatory effects [280,281]. The sources of soluble fibre are also recognized for their neuroprotective effects [282–286]. Therefore, it may be particularly challenging to consume enough fibres to preserve their health benefits, such as maintaining microbiome diversity, following a low FODMAP diet. Luckily, some foods, like oat bran, flax meal, chia seeds and psylium husk, are excellent source of soluble fibre with low FODMAP [287]. The profile of these foods might help in overcoming the current issues.

Low-carb diet

The ketogenic diet (KD) is a high-fat (55–60%), adequate-protein (30–35%), low-carbohydrate (5–10%) dietary intervention mainly used to treat refractory epilepsy in children [288,289]. Interestingly, mice treated with antibiotics or reared germ-free were found to be resistant to KD-mediated seizure protection, which was restored by the enrichment of *Akkermansia* and *Parabacteroides*. This effect was associated with reductions in systemic gammaglutamylated amino acids and elevated hippocampal GABA/glutamate levels [290]. Epilepsy and pain, especially neuropathic pain, share several pathophysiological mechanisms and often respond to similar pharmacotherapies [291,292]. It is also interesting to note that either neuropathic or visceral pain have been associated with a reduced abundance of bacteria belonging to *Akkermansiaceae* family [24,210]. KD has been reported to improve chronic pain in patients by neuroprotective effect [293], body weight reduction and an improvement of mood at the same time [294]. Indeed, KD may exert a protective role on mood disorders such as those induced by stress. The results reported by Sahagun et al., showed a kind of sexual dimorphism where ketogenic diet protect against chronic stress-induced reductions in plasma CORT and hypothalamic NPY expression more pronounced in female than in male rats. In both sexes, ketogenic diet feeding is protected by chronic stress-induced weight loss [295]. Anyway, under chronic stress conditions, the decreased availability of glucose in the brain is associated with impaired cognition. Indeed, it was shown a behavioural improvement albeit modest when the ketogenic diet chronically administered to rats was tested in the spatial memory test [296].

Fasting

A drastic dietary intervention with a therapeutic potential is the so-called 'Intermitting fasting', which involves alternating cycles with either no food or reduction in calories intake and cycles of unrestricted feeding [297,298]. It was reported to promote axonal regeneration after sciatic nerve crush in mice through an unexpected mechanism that relies on the gram-positive bacteria and an increase in the their metabolite indole-3-propionic acid in the serum [299]. It is also important to consider that in patients following therapeutic fasting, the intake of proteins dramatically increases, enhancing fermentation by colonic microbiota and

resulting in end-products such as polyamines [300], mainly spermine, spermidine, putrescine and cadaverine. Polyamines are considered mediators of nociception because they are endogenous regulators of ion channels vanilloid receptor 1 (TRPV1), acid-sensitive receptors and glutamatergic receptors. Accordingly, serum levels of spermine and spermidine were found to increase in patients affected by both chronic and episodic migraine, compared to healthy controls [301–303], and the suppression of polyamines from diet resulted effective against perioperative pain, in particular for the higher levels of pain [304,305]. Polyamine deficient diet can also counteract the phenomenon of tolerance and hyperalgesia associate with the use of opioids [306]. A diet reducing polyamine production gut microbiota (i.e. by selecting low polyamine-containing food or by reducing bacterial production of polyamines) was proposed as therapeutic target for chronic pain [307]. In contrast, the polyamine spermidine showed beneficial effects on neuropathic pain associated with chronic constriction injury in rodents [308]. Thus, polyamine's impact on nervous system is an aspect that deserves to be further investigated.

Conclusions

Diet manipulation is endowed of a great potential in the management of chronic stress and chronic pain conditions, and it is intriguing how most of the beneficial effects displayed by food constituents converge in the support of microbiota health (Table 1), in terms of both composition and metabolism and of gut–brain axis functionality. Although most of the gut microbiota-related literature has focused on the bacterial components, other microbes such as fungi, archaea, and viruses in the intestinal flora are involved in the maintenance of gut health [309–311], and they can be similarly affected by diet [312]. The influence of diet on these ecological niches might support the use of dietary intervention for preventing gut–brain axis disorders, like chronic pain and stress. Despite the fact that, in certain patients, concomitant financial, physical or psychological difficulties might pose an obstacle to the therapeutic employment of diet, chronic stress and chronic pain management might benefit from the support of dietitians skilled in the assessment, modification and support of diets specific to diseases.

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