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### ► To cite this version:

F Rul, C Béra-Maillet, M C Champomier-Vergès, K E El-Mecherfi, B Foligné, et al.. Underlying evidence for the health benefits of fermented foods in humans. *Food and Function*, 2022, 13, pp.4804 - 4824. 10.1039/d1fo03989j . hal-04345288v1

**HAL Id: hal-04345288**

**<https://hal.inrae.fr/hal-04345288v1>**

Submitted on 14 Dec 2023 (v1), last revised 15 Dec 2023 (v2)

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Cite this: *Food Funct.*, 2022, **13**, 4804

## Underlying evidence for the health benefits of fermented foods in humans

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Fermented foods (FFs) have been a part of our diets for millennia and comprise highly diverse products obtained from plants and animals all over the world. Historically, fermentation has been used to preserve food and render certain raw materials edible. As our food systems evolve towards more sustainability, the health benefits of FFs have been increasingly touted. Fermentation generates new/transformed bioactive compounds that may occur in association with probiotic bacteria. The result can be specific, advantageous functional properties. Yet, when considering the body of human studies on the topic, whether observational or experimental, it is rare to come across findings supporting the above assertion. Certainly, results are lacking to confirm the widespread idea that FFs have general health benefits. There are some exceptions, such as in the case of lactose degradation *via* fermentation in individuals who are lactose intolerant; the impact of select fermented dairy products on insulin sensitivity; or the benefits of alcohol consumption. However, in other situations, the results fail to categorically indicate whether FFs have neutral, beneficial, or detrimental effects on human health. This review tackles this apparent incongruity by showing why it is complex to test the health effects of FFs and what can be done to improve knowledge in this field.

Received 24th November 2021.  
Accepted 4th March 2022

DOI: [10.1039/d1fo03989j](https://doi.org/10.1039/d1fo03989j)

[rsc.li/food-function](https://rsc.li/food-function)

### 1. Introduction

For millennia, humans have consumed fermented foods (FFs). Fermentation was first used to preserve raw materials from microorganisms capable of causing disease or food alterations. FFs developed independently all over the world. Historically, the following foods have been most prevalent in different regions: dairy products in the Middle East, Europe, North and Central America, and India; plant-based foods in Korea, China, and Japan; cereal/plant-based foods in Africa; and both animal and plant-based foods in South America. More than 5000 FFs have been inventoried and mapped to date.<sup>1</sup> They represent a substantial percentage of our diets: 5–40% depending on the country and nutritional habits.

A broad range of FFs exist for several reasons. First, a wide variety of raw materials obtained from animals and plants

(*e.g.*, seeds, leaves, fruits, flour) yield a plethora of FFs. Second, there is great diversity in fermentation and fermentation-adjacent processes (*e.g.*, heating, grinding, pressing, oxygenating, enzymatic pre-digestion). Third, sociocultural practices differ greatly, as do the microbial communities that constitute food microbiotas, which are composed of bacteria and fungi (including yeasts). The growth and metabolic activities of these microorganisms transform raw materials physically and chemically *via* compound production, degradation, and modification. These processes modify the materials' organoleptic (*i.e.*, texture, taste) and technofunctional properties as well as their digestibility and nutritional qualities. However, FFs are unique because the microorganisms responsible for the above changes often survive and remain metabolically active, most frequently in the digestive tract. FF consumption appears to modulate the composition and metabolic activities of the gut microbiota.<sup>2</sup> That said, the full picture of how FFs affect overall gut microbiota functionality remains vague. The most promising health effects have been seen in the context of certain medical conditions, such as metabolic disorders.

Interest in FFs is currently booming, as evidenced, for instance, by the explosion of scientific publications and popular articles on the topic. This trend illustrates that the scientific community and consumers alike are increasingly drawn to the subject. Unfortunately, FFs are frequently touted as having broad health benefits in blog posts and knowledge-

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sharing platforms, where in-depth analysis and data-driven arguments are conspicuously absent. The aim of this review is to broadly explore how FFs could impact human health, taking into account the various microbes and raw materials involved, as well as examining their potential interactions. We present the current state of knowledge in the field and identify gaps in our mechanistic understanding of how FFs could affect human health. The objective is to pave the way for future studies, particularly in humans, that could properly test for the potential benefits of FF-based diets. The review's structure is outlined in Fig. 1.

## 2. Potential mechanisms underlying the health impacts of fermented foods

FFs are extremely diverse in type and composition (e.g., microbial, biochemical), which is a key reason why analysing their potential health benefits is a complex task. Additionally, it complicates our ability to identify the causal mechanisms at play. It is unquestionable that fermentation transforms the chemical composition and structure of raw materials in multiple beneficial ways. Indeed, it is essential to look beyond changes to the original matrix and also consider the biosynthesis of active molecules by microbes. Residual compounds can be important as well. These matrix transformations—both qualitative and quantitative—result from the metabolic and enzymatic activities of microorganisms. The microbiota of foods includes the microorganisms naturally found in the

matrix as well as any intentionally added starters. Common fermenters include lactic acid bacteria (LAB; *Lactobacillus*, *Bacillus*, *Micrococcus*, *Streptococcus*, *Pediococcus*, and *Leuconostoc* species), acetic acid bacteria (*Acetobacter*, *Gluconobacter*, *Gluconoacetobacter*, and *Komagataeibacter* species), and various fungi, including yeasts (*Saccharomyces cerevisiae* as well as *Pichia*, *Geotrichum*, *Zygosaccharomyces*, *Candida*, *Debaryomyces*, *Kluyveromyces*, *Aspergillus*, *Mucor*, and *Penicillium* species). The success of fermentation is dependent on the ability of such microorganisms to convert carbohydrates into organic acids and gas, which then transform and preserve animal and plant matter, reducing the risk that pathogen proliferation or spoilage will result. Food shelf life is concomitantly increased. It is thus evident that the presence of food microorganisms, whether alive or dead, is paramount to what occurs within the gastrointestinal tract (GIT) and underlies the health effects of FFs.

### 2.1. Contributions of food microorganisms

The potential health benefits of FFs are largely based on the different contributions made by microbes, whether within the food ecosystem or the consumer's microbiota. The bacteria and/or fungi in foods enter the GIT and temporarily become members of the consumer's endogenous microbial community,<sup>3</sup> resulting in certain effects. At this point, it is important to note that differences exist among traditional FFs, probiotic FFs (i.e., which have been inoculated with select microbial strains), and foods containing probiotics (i.e., the food serves as a vehicle).<sup>4</sup>

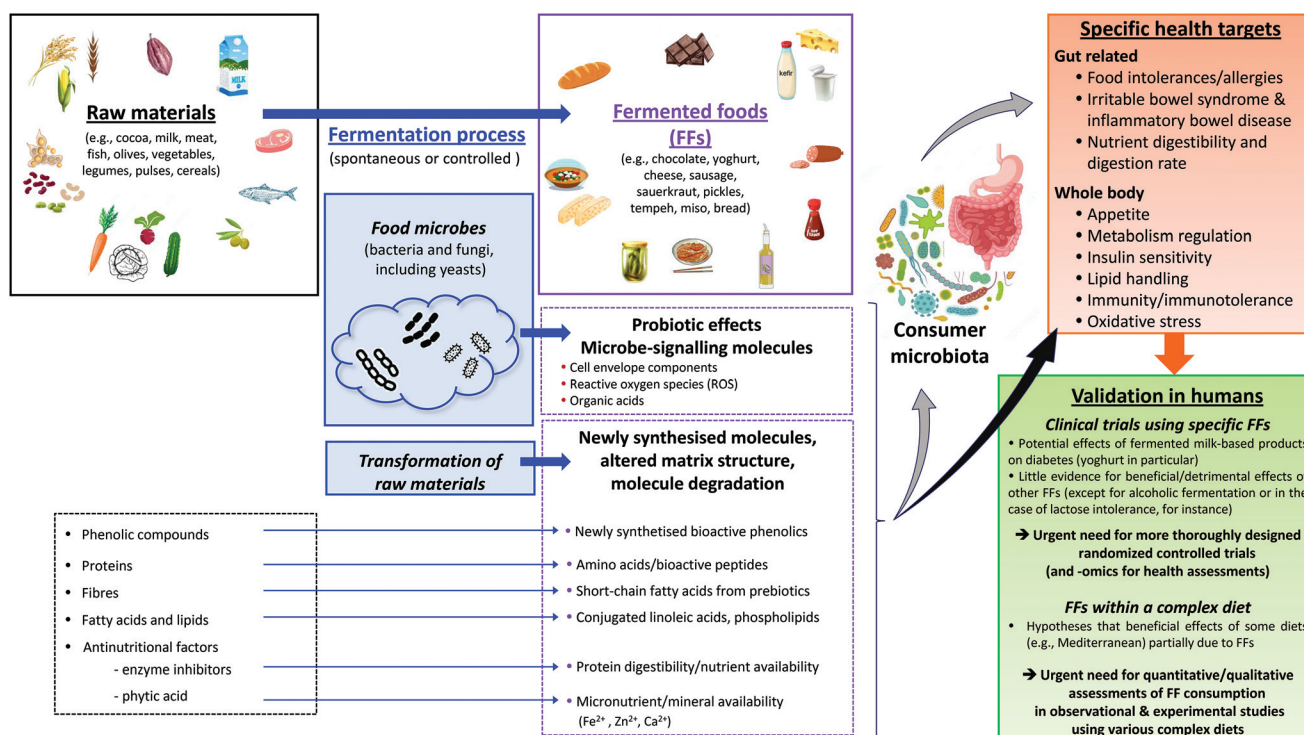


Fig. 1 Fermented food and potential mechanisms of action involved in their impact on health status.

First, FFs could have health effects by introducing microbes that modify the composition of consumer's microbiota,<sup>2,5,6</sup> a phenomenon with well-known impacts.<sup>4,7</sup> Mechanistically, such could result either from nutrient competition or selective bactericidal effects on pathobionts. That said, the spectrum of FF-derived bacteriocins and other antimicrobial molecules (hydrogen peroxide, organic acids) in the GIT are largely uncharacterised and should be explored in greater depth. Consequently, the  $10^8$  to  $10^{11}$  food microbes that humans ingest on average each day may indirectly serve to fine-tune and improve the intestinal microbiota's regulation of immune, metabolic, and neurotrophic functions by modulating the symbiont/pathobiont balance.

Second, FFs could deliver live microbes with direct putative probiotic effects that take highly diverse functional forms.<sup>8,9</sup> Many microbes isolated from FFs display and/or secrete compounds within biochemical classes likely to have probiotic characteristics. These include metabolites (short-chain fatty acids [SCFAs]); enzymes (bile-salt and glycoside hydrolases); other proteins; peptidoglycan degradation products (muropeptides); various structural exopolysaccharides; lipopolysaccharides with distinct immunogenicity; teichoic and lipoteichoic acids; glucans; and mannans.<sup>10–13</sup> The above signalling molecules are detected by the consumer's body and, together with those associated with the gut microbiota, are capable of having general or specific health effects.

Third, the microorganisms found in FFs could directly exert anti-inflammatory and/or antioxidative effects; strengthen the gut barrier; and influence other metabolic and neurological regulatory functions. Such can occur without any detectable shift in taxa within the resident microbiota and are clearly strain specific.<sup>14</sup> These effects are not linked to either species or food type, even if some species have consistently demonstrated promising properties.<sup>15,16</sup> For example, specific *Propionibacterium freundenreichii* strains (found in Swiss-type cheeses such as Emmentaler) can display anti-inflammatory properties,<sup>17</sup> and certain *Hafnia alvei* strains (found in Camembert or Italian stretched curd cheeses) appear to help with obesity-related disorders.<sup>18</sup> Health benefits can also be shaped by interactions among microbes within the food matrix, interference in metabolic activities (see § 1.2 below), and overall microbial abundance. Additionally, there is an influence of how well food bacteria interact with the gut and the consumer's microbiota, which is affected by the quantity and frequency of FF ingestion. The most common probiotics and allochthonous species do not permanently colonise the gut; they only persist for a few days.<sup>3,19</sup> However, dose and duration are key factors determining the persistence of health benefits.<sup>20</sup> Whether FFs can permanently seed bacteria in the gut microbiota remains an open question, one that includes a co-evolutionary perspective.<sup>6</sup>

Fourth, health benefits can be spurred even by non-viable forms of microorganisms. When considering cases in which FFs have been modified *via* technological processes, heating, and cooking, it is impossible to exclude the possibility that some previously released bioactive compounds and residual

inactivated/dead cells could still have certain post- and parabiological effects.<sup>13</sup>

Taken as a whole, these results seem to indicate that FFs are able to generate health benefits thanks to the sequential contributions of specific microbial strains that act either individually or as a group. That said, fully understanding the complicated microbial interactions taking place within food ecosystems and how food microbes interact with the dynamic and complex gut microbiota remains extremely challenging, as does identifying of the molecular mechanisms at play.

## 2.2. Production and supply of health-promoting compounds

**2.2.1. Bioactive peptide production.** First identified in dairy products, food bioactive peptides (BPs) occur in various FFs, such as those created from animal matrices (meat, fish, and shellfish) and plant matrices (namely pulses: cereals and pseudo-cereals). Research on this topic is prolific (*i.e.*, for recent reviews, see ref. 21–24). Food BPs are encrypted in food proteins from which they are released by the action of proteolytic enzymes over the course of fermentation or digestion in the GIT. Food microorganisms such as fungi and LAB play a major role in this process because they possess complete proteolytic systems,<sup>25</sup> which are composed of peptide transporters and numerous proteases, such as peptidases with *exo*- and *endo*proteolytic activities.<sup>25</sup> A particularity of FFs is that their BPs comprise both the products of proteolysis and peptides that were not consumed during microbe growth. BP quantity, composition, and bioactivity levels thus depend on protein matrix and microbial protease type, as well as on peptide consumption, which is linked to microbial peptide transporter specificity.

If they are to exert biofunctional effects, BPs must first make it past the gut proteases. They then need to be successfully absorbed by the intestinal epithelium to reach the circulatory system, which will distribute them throughout the body. Some research has found that BPs display resistance to *in vitro* gut digestion,<sup>26,27</sup> possibly because they have proline residues.<sup>28</sup> Such was observed *in vivo*, where the tripeptide Ile-Pro-Pro was recovered from human plasma.<sup>29</sup> Usually BPs are short (2–20 amino acids long) and rich in hydrophobic and/or charged amino acids.<sup>22</sup> In most, the composition of the N- and/or C-terminus plays an essential part in their functionality because this region interacts with cell membranes or important cell receptors.<sup>25,30,31</sup>

In those who consume FFs, BPs can modulate processes linked to different essential functions *via* their regulation of immune, opioid, thrombotic, oxidative, microbial, hypertensive, inflammatory, and/or carcinogenic activity.

The BPs that inhibit angiotensin-converting enzyme (ACE) are probably the best described. ACE catalyses the conversion of angiotensin-I (a peptide hormone) into angiotensin-II (a vasoconstrictor). Ultimately, ACE-inhibitory peptides can reduce blood pressure and thus have antihypertensive effects. They represent most of the BPs in milk,<sup>26,32–34</sup> of which the tripeptides Ile-Pro-Pro and Val-Pro-Pro are the most emblematic. They are also present in plant-based products, such as sourdough prepared from wheat, rye, and malt.<sup>35</sup> In rodents, the role of ACE-

inhibitory peptides has been observed following the consumption of fermented kefir<sup>36</sup> and fermented *Ruditapes philippinarum*;<sup>37</sup> the same has been seen in humans.<sup>38–42</sup>

BPs in fermented milk also have demonstrated antithrombotic<sup>27,43</sup> and anti-inflammatory properties.<sup>44,45</sup> Those found in milk or soy milk kefir can display hypolipidemic and weight management effects by modulating lipid metabolism. Rodent research suggests the specific mechanism is lipogenesis inhibition.<sup>46</sup> Some BPs have antioxidative properties,<sup>22</sup> especially those occurring in fermented milk: they boost the activity of antioxidative enzymes.<sup>47</sup> Cationic antimicrobial BPs have been found in kefir.<sup>24,48</sup> BPs with opioid activity occur in both milk-based and plant-based products; they possess a characteristic Tyr-X-Phe or Tyr-X-X-Phe N-terminus<sup>47</sup> that allows them to bind to opioid receptors. It is worth noting that fermented amaranth flour contains BPs that help block cancer cell growth,<sup>49</sup> a phenomenon that could be linked to the high peptidase activity of the LAB present. Interestingly, BPs in yoghurt appear to be involved in intestinal epithelial barrier protection. Indeed, in rats, the ingestion of one such BP increased goblet and Paneth cell number, which was associated with the greater expression of intestinal mucins and antibacterial factors (such as lysozymes).<sup>50</sup>

Thus, FFs contain myriad BPs with a broad range of functions, as has been seen in fermented milk<sup>33</sup> and soybean products.<sup>22</sup> Additionally, a single BP can display two or more functions,<sup>22</sup> as is the case for milk protein-derived BPs.<sup>45</sup> Given the exploding interest in consuming greater quantities of FFs, it is essential to invest more time and energy in exploring and characterising BPs. The search for BPs has been facilitated by the emergence of the new mass spectrometry methodologies and technologies. Furthermore, there are now dedicated BP databases, allowing faster identification *via* sequence similarities (e.g., BIOPEP <http://www.uwm.edu.pl/biochemia/index.php/en/biopep/32-bioactive-peptide-databases>).

**2.2.2. Transformation of phenolic compounds.** Plant-based foods are rich sources of numerous bioactive compounds, particularly dietary polyphenols, otherwise known as phenolics. The latter are at least partially responsible for the health benefits of diets rich in fruits and vegetables. Increasingly, phenolics are a focal point in human nutrition research. While they are not essential nutrients, phenolics do promote health because they contribute to the proper functioning of cells and organs, thus preventing or delaying the onset of diverse diseases, including cardiovascular conditions, type II diabetes, cancer, and declines in cognitive function.<sup>51</sup> Phenolics are compounds with at least one aromatic ring attached to one or more hydroxyl groups. They are classified into different families depending on chemical structure. The main groups include the phenolic acids, flavonoids, stilbenes, lignans, and curcuminoids. In plants, these compounds serve different functions, such as providing protection against ultraviolet radiation or microbial infections.<sup>52</sup>

Phenolics are well metabolised upon ingestion. In the small intestine, they can be absorbed by the epithelial cells, and like drugs and most xenobiotics, they then undergo phase II enzy-

matic metabolism, meaning they can be conjugated with glucuronic acid, sulphate, and methyl groups in the liver.<sup>53</sup> Most reach the large intestine, where they undergo complex modifications that generate low-molecular-weight metabolites. The latter can be efficiently absorbed *in situ*, and some undergo further phase II metabolism locally and/or in the liver before entering the circulatory system.<sup>51,54</sup> The absorption, distribution, metabolism, and excretion of phenolics has been extensively studied over recent years. One consistent pattern is that absorption is generally limited, particularly in the small intestine. However, in the large intestine, phenolics can be cleaved and metabolised by microbiota, generating metabolites that are potentially better absorbed.<sup>55</sup> The way in which a plant-based food is processed will differentially alter or degrade these compounds.<sup>56</sup> For example, fermentation shapes the phenolic profiles of plant-based foods by affecting the amount, bioaccessibility, and bioavailability of phenolics, which has functional benefits that take the form of antioxidant, antidiabetic, anti-inflammation, and weight management properties,<sup>57</sup> to name a few examples.

Soy is a key food ingredient in Asian cuisine. In Western countries, soybean products are mainly consumed by vegetarians because of soy's high protein content. Soy-based products are also versatile: they can be used to create meat and dairy substitutes. The major bioactive compounds in soybeans are isoflavones, which are classified as phytoestrogens. The most common isoflavones are genistein, daidzein, and glycitein.<sup>58</sup> Soy sauce is an example of a plant-based FF that is rich in bioactive compounds. It is traditionally made by mixing steamed, presoaked soybeans with roasted wheat flour. The mixture is then fermented using *Aspergillus oryzae* or *A. sojae* to produce koji.<sup>59</sup> The koji undergoes further fermentation, with the predominant microbial community switching from filamentous fungi to halotolerant LAB, including *Weissella*, *Lactobacillus*, *Streptococcus*, and *Tetragenococcus* species, as well as acidophilic yeasts, such as *Zygosaccharomyces rouxii*, *Candida etchellsii*, and *C. versatilis*.<sup>60</sup> Thus, soy sauce is not only a seasoning. It is also a potentially functional food, as the nutritional value of the fermented soy products is higher than that of non-fermented soy products.<sup>61</sup> In animal models, its health benefits include antidiabetic, antioxidative, anti-inflammatory, anticarcinogenic, and antihypertensive activity, to name a few examples.<sup>62</sup> The fermentation of soy-based products can increase the bioavailability of isoflavones.<sup>63</sup> For example, the fermentation of soy milk results in the  $\beta$ -glucosidase-mediated hydrolysis of daidzin and genistin into daidzein and genistein, respectively, with bioavailability climbing by as much as 97%.<sup>63</sup>

Cocoa is another example of a fermented phenolic-rich food. Cocoa beans must be fermented to produce flavourful and full-bodied cocoa.<sup>64</sup> Fermentation generally occurs on cocoa bean farms – where it is still a spontaneous process – which results in pronounced variability in end product quality. It involves three main microbial groups: yeasts, LAB, and acetic acid bacteria.<sup>64–66</sup> Fermentation modifies the phenolics in cocoa beans in important ways, which may or may not be

beneficial. It has been suggested that new bioactive compounds emerge that can form phenolic-protein binding complexes.<sup>67</sup> Several studies have shown that metabolites produced by bacteria and fungi during fermentation underlie the health-promoting properties of dark chocolate and other cocoa-derived products that had previously been attributed to cocoa flavonoids and methylxanthines.<sup>65,68</sup> There are other examples of phenolic-rich FFs. For instance, fermented whole-grain sorghum was found to contain higher levels of catechin, gallic acid, and quercetin, which might be attributable to the activity of *Lactobacillus* strains.<sup>69</sup> An increase in total phenolic content in whole-grain millet-based koji has also been observed, which might result from phenolics being freed by the activity of fermentation-produced enzymes.<sup>70</sup> When naturally present bacteria, including LAB, are involved in the fermentation of commonly consumed legumes, such as black-eyed peas, kidney beans, and lentils, total phenolic content can increase, probably because phenolics go from bound to soluble, which suggests that legume fermentation increases their bioavailability.<sup>71</sup> The result has been greater reducing power, free radical scavenging, and lipid peroxidation inhibition in fermented *versus* unfermented samples.

Taken together, the above results indicate that fermentation can increase the nutritional value of plant-based foods that are rich in phenolics and other bioactive compounds. Such is achieved *via* the release of phenolics by cell-wall-degrading enzymes. Moreover, fermentation can lead to the conversion of bioactive compounds *via* different pathways, including glycosylation, deglycosylation, ring cleavage, methylation, glucuronidation, and sulphate conjugation, which can all increase metabolite bioavailability and consequently impact human health. It should be noted that recent research has observed a significant reduction in natural levels of phenolics during fermentation and roasting, which can lead to improved bioactivity.<sup>72</sup>

### 2.2.3. Dietary fibres and fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs)

**2.2.3.1. Dietary fibres.** There are documented health benefits associated with the naturally occurring plant carbohydrates, and in particular dietary fibres (DF) found in various types of cereals, fruits, vegetables, and legumes. The Codex Alimentarius (FAO–WHO) defines dietary fibres as polymers made up of at least 10 monomers that are neither digested by host enzymes nor absorbed in the human small intestine.<sup>73</sup> Since 2009, it allows national authorities to include oligomers with a degree of polymerisation (DP) 3–9 as DF, and this has been adopted by many countries worldwide. DFs affect human health *via* their composition and physiochemical properties, which lead to shifts in gut microbiota composition and impacts on consumer metabolism. They serve as carbohydrate sources for the intestinal microbiota. DFs are first broken down into smaller molecules by Carbohydrate-Active enZymes (CAZymes),<sup>74</sup> which are produced by fibrolytic bacteria species. They are then transformed *via* fermentation into SCFAs, which help maintain host energy and intestinal homeostasis,<sup>75,76</sup> among other

functions. Furthermore, DF consumption promotes bacterial richness in the gut microbiota and decreases the risk of inflammatory and metabolic diseases.<sup>77,78</sup>

DFs fall into different polymer categories. For example, among those with more than 10 monomers are the (i) high-molecular-weight soluble and insoluble fibres, which are largely non-starch polysaccharides (NSP) such as hemicellulose, pectin, cellulose,  $\beta$ -glucan, lignin, the gums, and the mucilages, which are embedded in a complex matrix structure; (ii) the resistant starches; and (iii) the synthetic analogues, such as polydextrose, and dextrins.<sup>79</sup> DFs can also be oligosaccharides, including the xylo-oligosaccharides (XOSs), galacto-oligosaccharides (GOSs), and fructo-oligosaccharides (FOSs). These compounds, along with lactose, fructose and polyols are often referred to as FODMAPs, which stands for Fermentable Oligo-, Di-, Monosaccharides, and Polyols.

In FFs, microbial enzymes first break down non-digestible cellulose and hemicellulose-containing structures such as seeds or grains and release the nutrients surrounded by plant cell walls, improving their digestibility.<sup>80</sup> Phenolics bound to carbohydrate residues in fruits and vegetables can also be detached from polysaccharides *via* the action of microbial enzymes, resulting in the release of bioactive compounds. Typically, the natural fermentation of cereals decreases the levels of carbohydrates (namely polysaccharides and resistant oligosaccharides).<sup>81</sup> Such is the case for starch in millet varieties.<sup>82</sup> Starch is the major carbohydrate found in cereals and legumes. During fermentation, it is converted to maltodextrins and simple sugars *via* the hydrolysing action of  $\alpha$ -amylase and maltase. Glucose is a readily accessible carbon resource for most of the microbial starters used to launch fermentation. During breadmaking processes with yeast or sourdough (a mixture of bacteria and yeast) fermentation, rye fructan levels are significantly reduced, and  $\beta$ -glucan is degraded.<sup>83</sup> Fermentation thus enhances the digestibility of carbohydrates in foods.

Sugars are fermented *via* different strain-dependent metabolic pathways, leading to the production of bioactive compounds such as organic acids and alcohol. For example, in yoghurt, 20–40% of the lactose present in milk is transformed into lactic acid.<sup>84</sup> Volatile compounds (VOCs) like acetate and ethanol are generated from glucose by lactic starter cultures, and their levels are correlated with food product sensory characteristics.<sup>84</sup> Among the VOCs produced during food fermentation are the SCFAs acetate, propionate, and butyrate found in yoghurt,<sup>84,85</sup> cheeses,<sup>86</sup> fermented rice,<sup>87</sup> vegetables and cocoa,<sup>64,88</sup> and soy and rye drinks,<sup>89</sup> usually at higher levels than those seen in the unfermented raw materials.<sup>90</sup> The SCFAs in FFs could act in tandem with the SCFAs produced by autochthonous intestinal bacteria to maintain homeostasis.<sup>91</sup> An increasing number of studies have been exploring associations between raw substrates and microorganisms to optimise SCFA profiles and levels in consumer products. The fermentation of carbohydrates thus boosts quantities of bioactive compounds. Consequently, raw materials rich in DF and simple sugars could yield better-quality FFs. Furthermore, *Lactobacilli*

and Bifidobacteria express several  $\beta$ -glucosidases that make them good candidates for starters.

From a nutritional perspective, sourdough fermentation, which combines the action of LAB and yeasts, can improve the nutritional properties of wheat by lowering a bread's glycaemic index<sup>92</sup> and reducing post-prandial glucose and insulin responses in healthy individuals.<sup>93</sup> Indeed, the lactic acid produced by LAB acidifies the dough and lowers starch digestibility by inhibiting amylolytic enzymes, which are also unable to break down the interactions between starch and gluten. Compared to refined wheat soft bread, fermented whole-grain rye crisp bread increased satiety by 20–30% in healthy adults, a difference that was linked with quantities of arabinoxylans and  $\beta$ -glucan, both DFs.<sup>94</sup> Yoghurt is the only FF for which health claims have been validated by the European Food Safety Authority (EFSA).<sup>91</sup> Indeed, yoghurts are generally well tolerated even by lactose-intolerant people because the associations of live bacteria (*L. delbrueckii* ssp. *bulgaricus* and *S. thermophilus*) synthesise  $\beta$ -galactosidases, which hydrolyse lactose both during yoghurt making and during gut transit.<sup>95</sup> Similarly, LAB fermentation of legumes (e.g., soy) leads to the enzymatic hydrolysis of indigestible  $\alpha$ -galactosides such as raffinose and stachyose, which are normally metabolised by gas-producing bacteria in the large intestine, creating disorders such as flatulence.<sup>96</sup> Finally, overweight and obese patients have experienced potential health benefits (e.g., improved metabolic measurements) after consuming kimchi, a traditional Korean LAB-fermented vegetable mixture composed of napa cabbage, red pepper, garlic, green leeks, and ginger that is thus rich in DFs.<sup>97</sup>

**2.2.3.2. FODMAPs.** More recently, research has turned to exploring the possible health effects of dietary FODMAPs. FODMAPs are naturally present in the foods we eat, but they are also frequently employed as food additives. The use of fructans (e.g., inulin, chicory root extract, fructo-oligosaccharide) is especially common; these compounds could potentially be broken down by ileomucosal bacteria.<sup>98</sup> FODMAPs are defined by molecular size (although there is no precise limit on chain length), degree of absorption in the small intestine, and fermentability.<sup>99</sup> They are poorly absorbed in the small intestine or remain entirely undigested. Thus, they can either have beneficial prebiotic effects on the intestinal microbiota and contribute to intestinal homeostasis and health, or they can cause gastrointestinal symptoms in people suffering from irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). The latter result from fermentation by the intestinal microbiota, water retention, and flatulence.<sup>99</sup> Recent studies in rats, mice, and humans have indicated that FODMAPs might indeed harm the colon by causing reversible changes to mucosa structure and function, increasing intestinal permeability, and decreasing the barrier effect.<sup>99</sup>

Thus, people are increasingly reducing dietary FODMAPs by selecting ingredients that are low in fermentable carbohydrates.<sup>100</sup> In a randomised clinical trial conducted with IBS patients, the reduction of FODMAP content in wheat and rye breads *via* sourdough fermentation improved digestive health

and seemed to increase FODMAP tolerance.<sup>101</sup> Carbohydrate levels are low in FFs such as kombucha, kefir, yoghurt, hard cheeses, chutneys, and fermented vegetables (e.g., sauerkraut, pickles, salsas, and carrots). Over the last few years, several studies have shown the effectiveness of a diet-based treatments.<sup>102</sup> A low FODMAP diet was found to reduce the abundance of Bifidobacteria and *Clostridium* cluster XIVa bacteria while increasing the abundance of *Ruminococcus*.<sup>103</sup>

One emerging area of research is developing biotechnological tools for lowering FODMAP levels in food ingredients and products. In breads, yeast fermentation has shown some promise in reducing levels of fructans (by 56–90%) as well as those of other FODMAPs<sup>104</sup> without modifying bread properties and nutritional qualities. Sourdough fermentation is a reliable method for reducing FODMAPs in bread and for generating high-quality bread products that also meet special dietary requirements.<sup>96</sup> Produced *via* extended fermentation times, such breads are also fit for consumption by individuals with IBS.<sup>100</sup>

In conclusion, the fermentation of DFs and FODMAPs is a suitable strategy for improving the carbohydrate availability, digestibility, and nutritional value of food products (especially *via* bioactive compounds, namely SCFAs). The result is food products with functional properties and health-related benefits.

**2.2.4. Production of conjugated linoleic acids and polar lipids.** Fermentation may directly alter food lipid levels, as observed as early as 1964 in the case of dill pickles.<sup>105</sup> It thus (i) modifies the fatty acid (FA) profiles of animal- and plant-based foods<sup>106–109</sup> and/or (ii) generates bioactive lipids with potential health effects (e.g., antibacterial or antioxidant properties<sup>110–112</sup>). Notably, fermentation can increase levels of SCFAs (see above) (e.g., in traditional Polish cheeses<sup>113</sup>). The same is true for  $\gamma$ -linolenic acid (GLA, C18:3 *cis*-6,9,12), whose quantities can climb following the fungus-mediated fermentation of blackcurrants<sup>114</sup> or soybeans (douchi, tempe),<sup>114,115</sup> for example. Here, we focus on two bioactive lipids of particular interest, namely conjugated linoleic acids (CLAs) and polar lipids.

CLAs have been found to display various strong, isomer-specific physiological effects *in vivo*, including weight management, antidiabetic, and antihypertensive properties<sup>116</sup> as well as anti-inflammatory and anticarcinogenic properties.<sup>117</sup> Many food-grade bacteria commonly found in dairy products and widely used as FF starters (e.g., Bifidobacteria, LAB, and Propionibacteria) can convert linoleic acids (LAs, C18:2 n-6) and linolenic acids (LNAs, C18:3 n-3 isomers) to CLAs and conjugated LNAs, respectively.<sup>118,119</sup> Linoleate isomerase activity is responsible for this conversion and is strain dependent.<sup>118</sup> Bioactive doses of CLAs appear to be above 1 g d<sup>-1</sup>, which is too high to be achieved *via* the moderate intake (i.e., 1–2 servings) of natural food sources. As a result, there is research interest in identifying alternative strategies for fortifying foods, notably utilising fermentation.<sup>120</sup>

CLAs have been produced from LAs (70% rumenic acid) *in vitro* by Propionibacteria<sup>121</sup> and in fermented dairy pro-

ducts, where the *cis*-12 double bond in LNA is isomerised.<sup>117</sup> CLA levels were found to be higher in hard sheep milk cheeses than in hard cow and goat milk cheeses.<sup>122</sup> They can be further increased using autochthonous CLA-producing *Lactobacilli* strains.<sup>123</sup> CLA-producing capacity was also identified in *Lactobacilli* in conventionally prepared Indian dairy products (namely dahi and lassi); production levels can vary 1- to 3-fold depending on the strain.<sup>124</sup> Their use has been proposed as a means for enhancing CLA production during the fermentation of ground beef, semidry sausages, and Turkish-style sucuk (e.g., by 8–38 mg g<sup>-1</sup> of fat in fermented beef).<sup>125–127</sup>

CLA can also be generated by LAB in sauerkraut and fermented cabbage<sup>128</sup> or by *P. freudenrichii* in plant-based by-products stemming from blackcurrants, oats, okara, and camelina meal, giving rise to nutraceutical possibilities.<sup>129</sup> Several studies found that certain *L. plantarum* strains isolated from naturally fermented Chinese pickles and sauerkraut showed a marked capacity for converting LAs into CLAs (rate of up to 25%).<sup>128,130</sup> CLA isomer profiles can differ depending on the food,<sup>125,130,128</sup> Other research discovered that *L. paraplantarum* D2-1, isolated from fermented vegetables, is a promising probiotic that could potentially be exploited in soy milk fermentation, given the microbe's ability to generate CLAs.<sup>131</sup> The *L. plantarum* strains S48 and P1201 both increased levels of phenolics, aglycone, and CLAs (90% *cis*-9, *trans*-11 isomer) in soy yoghurt, resulting in interesting antioxidative effects *in vitro*.<sup>132</sup> Effects were even further enhanced when a mixture of *L. plantarum* and *L. brevis* was used.<sup>133</sup>

Endogenous microorganisms in the milk matrix can impact phospholipid (PL) levels. During the production of quark cheese from buttermilk, PL content rose by 21.5%, which was attributed to the proliferation of the inoculated LAB, whose membranes are also made of PLs.<sup>134</sup> Similarly, higher PL levels were observed in goat milk yoghurt *versus* goat milk, where the source material was obtained from confined (*i.e.*, not grazing) animals.<sup>135</sup> Some LAB can also metabolise PLs. *Pediococcus acidilactici* isolated from Gouda cheese contains a PL-hydrolysing phosphoesterase that may enhance the digestibility and intestinal absorption of PLs.<sup>136</sup> Furthermore, sphingomyelin from milk fermented by LAB (*L. delbrueckii* subsp. *bulgaricus* 2038 and *S. thermophilus* 1131; in a PL concentrate) *versus* from unfermented milk was more readily absorbed by the intestines in rats.<sup>137</sup> Lordan *et al.* identified several genes associated with PL biosynthesis in a wide range of ovine yoghurts (*i.e.*, produced using different LAB starter mixtures).<sup>138</sup> In yoghurt PL fractions applied to platelets *in vitro*, fermentation-mediated alterations in lipid profiles (e.g., increased levels of phosphatidylethanolamine, sphingomyelin, phosphatidylcholine, and other compounds) went hand in hand with increased antithrombotic properties.<sup>139</sup> There are clearly new research questions related to the impacts of fermentation on PL metabolism and health that remain to be answered. Given that PLs are also present in plant-based products and by-products, the need exists for further research on how fermentation impacts plant matrices.

### 2.3. Degradation and elimination of deleterious compounds

**2.3.1. Antiallergic properties of fermented foods.** Food allergies seem to be increasing in prevalence worldwide over recent decades. They currently affect 2–5% of the general population (1–5% of adults and 4–8% of children<sup>140</sup>). Generally, the digestive system, and especially the gut immune system, is fairly tolerant of the food proteins we ingest. Food allergies tend to occur when there is a malfunction in the oral immunotolerance of a specific food antigen (*i.e.*, an allergen), which leads to abnormal immune reactions by allergen-specific IgE antibodies. Repeated exposure to the allergen is required to provoke clinical allergy symptoms, which are mediated *via* mast cell activation.<sup>141</sup> Several studies have found a strong association between gut microbiota diversity and the ability to tolerate and recover from food allergies.<sup>142</sup> As mentioned above, diet type and composition can strongly influence microbiome diversity and composition.<sup>6</sup>

Although FF consumption is resurging in Western societies, it remains rare to see large-cohort studies exploring the effects of consuming such foods on atopy (e.g., atopic dermatitis [AD], eczema, and rhinitis) and the development of food allergies. The most relevant studies have focused on the influence of ingesting isolated probiotic strains. In randomised controlled trials (RCTs), supplements containing *L. rhamnosus* GGL and *L. rhamnosus* HN001 were given to women during pregnancy and both to women and their infants after birth; the treatment resulted in a 50% reduction in AD and eczema in the study's high-risk population.<sup>143</sup> Probiotic effects arise from immunomodulatory mechanisms that aid in the recovery of oral tolerance *via* the regulation of CD103 dendritic cells, the suppression of mast cell activation, and the modulation of microbiome composition and diversity.<sup>144–147</sup>

A few studies have explored whether whole fermented food matrices display antiallergic properties. The most frequent object of study is fermented milk. Research has explored how to reduce responses to milk allergens and both prevent and treat cow's milk allergies. Recently, Wróblewska *et al.* demonstrated that yoghurt enriched with *L. plantarum* and/or *Bifidobacterium lactis* elicits low immunogenic reactivity towards key milk allergens (caseins/whey proteins) and that the modified allergens skew the immune profile from Th2 (allergic) to Th1 (tolerance) responses in a murine model for milk allergies.<sup>148</sup> Additionally, yoghurt consumption has been shown to have protective effects in infants with milk allergies (<2 years old); however, children with an immediate allergy (*i.e.*, IgE mediated) did not tolerate yoghurt and performed poorly in an oral food challenge compared to children with a delayed milk allergy (*i.e.*, non IgE mediated).<sup>149</sup> Obviously, it is difficult to extend conclusions obtained with preclinical models to humans. Future work should investigate the effects associated with different fermented cow's milk products (e.g., milk, cheese, and butter), the type of allergic reaction (*i.e.*, immediate/delayed), and strain specificities.

Interestingly, much attention has been paid to the antiallergic properties of Asian fermented foods. In a cohort study



involving healthy Koreans with AD (9763 adults), researchers looked at how the ingestion of different local FFs (kimchi, doenjang, chungkookjang, and fermented seafood) affected AD development.<sup>150</sup> There was a negative correlation between FFs and AD prevalence. It was then hypothesised that the presence of different metabolites ( $\gamma$ -aminobutyric acid and *ortho*-hydroxydaidzein) and *L. plantarum*, *L. sakei*, and *Weissella cibaria* WIKIM28 in the FFs protected against AD development, given that the metabolites and bacteria are known to effectively modulate the immune system.<sup>151,152</sup> In addition, using a murine allergy model, Hong and Chen demonstrated that the consumption of heat-inactivated *L. kefirifaciens* M1 isolated from kefir grains could block IgE production following an *in vivo* ovalbumin (OVA) challenge and could increase Th1 cytokines (*i.e.*, promote a tolerance profile).<sup>153</sup> The results of all these studies highlight the potential therapeutic or preventive use of FFs in the context of food allergies or food allergy symptoms.

Furthermore, using LAB with high levels of proteolytic activity as starters when fermenting foods could help temper product allergenicity. They can decrease the number of allergenic epitopes (*i.e.*, immunoreactive oligopeptides 8 to 12 amino acids long) formed during fermentation and thus reduce the allergenicity of many food types, including that of milk, soybeans, wheat, shrimp, cashews, and sesame seeds.<sup>144,154–158</sup>

**2.3.2. Antinutritional factors.** When it comes to FFs, another topic of interest is the presence of antinutritional factors (ANFs) in foods. ANFs can limit the bioavailability of essential nutrients (*i.e.*, vitamins, minerals) and impair food digestibility (*e.g.*, that of proteins, carbohydrates), which can lead to declines in nutritional value and, in some cases, render a food unsuitable for consumption. ANFs naturally occur in legumes, cereals, pseudocereals, and food crops in general. Examples include phytic acid, tannins, enzyme inhibitors, saponins, and lectins; ANF types and amounts vary across plant species.<sup>159</sup> Reducing ANF concentrations in foods is a major concern in the field of human nutrition. Fermentation is one of the most efficient and inexpensive processes that can be used to accomplish this task (for recent reviews, see ref. 159–164). It has been successfully applied to numerous plant materials, including cereals, maize, and sprouted flours<sup>165,166</sup> as well as legumes,<sup>167–169</sup> by exploiting the microbial activity of naturally occurring or inoculated LAB and fungi. ANFs can thus be transformed into more easily assimilated compounds (*e.g.*, proteins), and/or trapped micronutrients can be freed.

Ubiquitously found in plants, phytic acid is a major ANF in plant-based foods. It forms complexes with proteins, leading to their decreased digestibility in the GIT. In addition, because of its reactive phosphate groups, it strongly bonds to minerals,<sup>170</sup> reducing their bioavailability *via* chelation. Humans lack phytase in their GITs, which means that the gut's access to minerals ( $\text{Ca}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Fe}^{2+}$ ) is largely determined by how well food microbes can degrade phytic acid. Phytase activity is boosted by the pH values of FFs.<sup>159,171</sup> A significant reduction in phytic acid levels (by 20–90%) has been observed in ferment-

ed cereals,<sup>8,172,173</sup> in soybeans and kidney beans fermented with *R. oligosporus*,<sup>174</sup> in soybeans and green peas fermented with bacteria,<sup>164</sup> and in cassava fermented with a *S. cerevisiae*-*L. bulgaricus* association.<sup>175</sup>

Another major ANF type found in plants is enzyme inhibitors, which suppress the action of GIT enzymes (*i.e.*, proteases such as trypsin and chymotrypsin or  $\alpha$ -amylases). By blocking the active sites of GIT enzymes, enzyme inhibitors slow down protease activity, thus limiting protein digestion. These inhibitors are more abundant in legumes than in cereals.<sup>170</sup> They have been successfully degraded by utilising food microorganisms at different, pronounced levels in sourdough<sup>176,177</sup> and legumes<sup>178</sup> (*e.g.*, in fava bean flour fermented with *L. plantarum*<sup>167</sup> or in tempeh<sup>161</sup>). Combining fermentation with cooking can significantly boost this effect: a 99% decrease in trypsin inhibitors in grass peas has been reported.<sup>179</sup>

Lastly, plant-based foods contain certain tannins (which are phenolics) that can have adverse effects because they form insoluble complexes with divalent ions (*e.g.*, iron, zinc, or copper) as well as with proteins and carbohydrates. Therefore, the digestibility of these compounds is reduced, especially that of proteins<sup>180</sup> because of protein aggregation. Fermentation, particularly by LAB, has been found to effectively reduce tannin levels in sourdough fermented with *Lactobacilli*,<sup>176</sup> in cassava-based products fermented with *S. cerevisiae* and *L. bulgaricus* subsp. *bulgaricus*,<sup>175</sup> in fava bean flour fermented with *L. plantarum*,<sup>167</sup> and in fermented cereals and pseudocereals.<sup>181</sup>

In conclusion, in FFs, microorganisms show great promise in being able to reduce and even eliminate ANFs. As a consequence, food nutritional value can be greatly improved by increasing mineral availability and protein digestibility.

## 2.4. Concluding remarks

This review has underscored that microbial fermentation is an efficient means for increasing the nutritional quality of foods, by boosting potentially beneficial compounds and limiting potentially deleterious ones. To improve upon the benefits of fermentation, other processes can be exploited in tandem, such as heating, seed germination, milling, soaking, applying enzyme treatments, and extruding matrices.<sup>159,170,171</sup> To build on the probiotic effects of FFs, future research could further investigate the potential of different microorganisms and microbial strains, by examining their various metabolic activities and biofunctionalities when they occur individually and within associations. We must gather more detailed knowledge on the microorganisms present (metagenomics), their physiology/behaviour (metatranscriptomics, metaproteomics), and their production of metabolites (metabolomics). Overall, the use of combined techniques (an approach that is already spreading) will make it easier to improve the health-promoting potential of FFs and design new and improved versions with specific nutritional properties that are tailored for specific populations (*e.g.*, the elderly, people with metabolic diseases, people with allergies). Of course, FF properties are highly dependent on (i) the initial composition of the food matrix,

which shapes the fermentation process, and (ii) the composition and activity of the microbial community associated with the food.

### 3. Health benefits of fermented foods that have been validated in human studies

Over recent years, the health impacts of FFs have been extensively studied, reviewed, and debated.<sup>4,8,104,182–185</sup> Most research has been focused on nutrition-related pathologies or metabolic impairments. For example, particular attention has been paid to the effects of FFs in the context of obesity,<sup>186</sup> metabolic syndromes,<sup>97</sup> diabetes,<sup>187,188</sup> cardiovascular diseases,<sup>188,189</sup> and hypertension.<sup>190</sup> There have also been studies documenting the health effects of FFs in relation to gut health (*e.g.*, allergies,<sup>158</sup> food intolerance,<sup>191</sup> inflammatory diseases [IBS, ulcerative colitis] affecting the small intestine and colon<sup>192–194</sup>). Lastly, a smaller body of literature exists on the potential anticarcinogenic properties of FFs (most frequently in relation to GIT cancers; for a review, see ref. 182) and the impacts of FFs on the gut-brain axis (*i.e.*, anxiety, cognitive function).<sup>195,196</sup>

#### 3.1. Preliminary considerations

The health impacts of FFs have been studied *in vitro* and in various animals, mainly mice, rats, and humans. However, it is crucial to note that results observed *in vitro* or in non-human animals are not always seen in humans for the reasons detailed below. This discrepancy could cause confusion regarding the health effects of FFs that have been validated in humans. Therefore, the following discussion is based exclusively on the latter.

To date, both observational and experimental studies have been carried out in humans to determine whether dietary habits or components have beneficial or adverse health effects. In the case of human populations, it is important to carry out a reasonable number of studies to be able to reliably evaluate the potential impacts of food products.<sup>197,198</sup> One way to validate the health effects of a given food type is to properly characterise the nature of the FFs involved (*e.g.*, in terms of macro- and micronutrient composition and quantity, the microorganisms present, matrix structure). Such an approach limits the sources of variability in responses across studies, facilitating comparisons. In observational studies, it is also crucial to carefully assess consumption of FF products or product families. This latter point is particularly important in longitudinal cohort studies, where dietary assessments/records do not necessarily reveal the full breadth of FF consumption. With the exception of studies involving fermented dairy products (*e.g.*, yoghurt, cheese), detailed records of FF intake are rare. Their availability depends greatly on the target population, its geographical location, and its typical nutritional habits. Lastly, assessing the health impacts of FFs requires properly evaluating health status and health targets. Such necessitates that health outcomes be explicitly defined from the beginning and that appropriate, validated markers and phenotypes be employed. Again, this consistency facilitates study comparisons, particularly in the context of *meta*-analyses or select literature reviews.<sup>4</sup> Indeed, animal studies may more easily demonstrate the benefits of FFs because they can utilise more comprehensive and invasive methodologies, which allows for a greater degree of consistency.

Another essential facet to consider when evaluating the health effects of FFs is the choice of the control group. Table 1 summarises the different types of control groups that have been used in various studies. As should be obvious, the choice of the control can have major consequences when interpreting

**Table 1** Examples of experimental designs that have been used to study the potential health effects of FFs. The goal of this table is to guide control group choice based on the research question

Control	Comparison type
Diet without FF	Effect of FF as a whole <i>Any effects observed might result from the fermentation process, the food itself, and/or the food's macro- and micronutrient levels</i>
Diet with unfermented raw materials	Effect of FF as a whole <i>Any effects observed might result from the fermentation process (e.g., presence of certain bacteria and/or their metabolites) or the resulting food matrix (i.e., fermentation can alter food structure, further modifying digestion)</i>
Diet with FF where microorganisms have been killed	Probiotic effects <i>Any effects observed might come from the living bacteria alone (except if the process used to kill the bacteria has altered matrix structure and/or food composition)</i>
Food subject to a chemical, enzymatic, or physical treatment that helps mimic the FF matrix	Fermentation effects including microorganisms and their products <i>The intent is to control for any matrix effects</i>
Diet supplemented with bacteria present in the FF	Probiotic effects alone <i>There are no interactions with the food/mechanistic studies</i>
Diet containing FF as probiotic supplement	Probiotic effects combined with food effects
Diet in which the hypothesised bioactive compound is added	Effect of a specific compound <i>Mechanistic studies focused on the functional effects of FFs on the consumer (via fermentation metabolites)</i>
Diet in which FF quantity varies (low vs. high)	Dose effect

the research results. It can explain a variety of issues seen in the literature, including potential confounding factors and the extreme variability of the results. Additionally, control group choice will, by necessity, differ based on the food under investigation. Indeed, while fresh (or acidified) milk is a good control in research involving fermented milk, the unfermented versions of some plant-based products may be inedible for a variety of reasons (*e.g.*, because of a disagreeable flavour, the presence of ANFs, poor digestibility).

In such cases, it is common to employ the FF as a supplement, eschewing any certainty that potential health benefits result from factors associated with the fermentation process, the macro- and micronutrients present in the raw materials, or both.

The above considerations are required if one wishes to determine whether or not specific FFs have health effects. However, it is also possible to decipher whether an FF as a whole in the diet has health benefits. While this question can be difficult to address in observational studies, given that obtaining detailed, long-term records of FF consumption is complex (see above), some more detailed experimental studies have had better success. For example, Wastyk *et al.* demonstrated that increased FF consumption improved microbiota diversity as well as the values of immune response and inflammatory markers;<sup>199</sup> the FFs varied greatly in type (from yoghurt to kimchi), and the increase in intake was pronounced (from nearly zero to 5–10 daily servings for 6 weeks). It is interesting to note that the beneficial effects observed after 6 weeks of the FF treatment cannot be attributed to altered macro- or micronutrient intake, as there were no differences in dietary levels of calories, total protein, fibre, fat, and saturated *vs.* unsaturated fats. The only exception was that animal proteins increased after the treatment. Such results are very promising and tend to support the idea that FFs have beneficial immune effects in individuals who were initially eating a Western diet with below-recommended levels of fibre. Of course, and as underscored by the researchers themselves, it is important to see if such benefits also occur in individuals with chronic diseases or immune system pathologies.

### 3.2. Beneficial health effects of fermented foods: the special case of dairy products

Fermented dairy products are by far the most studied FFs. They have been the subject of several *meta*-analyses and select literature reviews. One challenge is that dairy products form a large family—some are fermented (*e.g.*, yoghurt, cheese), while others are not (*e.g.*, milk). Their health effects have been widely studied because of the debate surrounding their levels of saturated fatty acids and their potential impacts on cardiovascular diseases or type 2 diabetes, in particular.<sup>200–202</sup> Consequently, many cohort-based studies of an observational or experimental nature have been conducted, and a number of *meta*-analyses and select literature reviews have examined dairy products both in general and at more specific levels. The main focal products have been milk, yoghurt, cheese, and, to a lesser extent, kefir. Still, because dairy products are consumed in much smaller quantities in Asia than in Europe or North

America, the results obtained in these regions might not necessarily apply to the general world population.<sup>203</sup>

Overall, the consumption of dairy products has been associated with increased, decreased, and unchanged rates of overall mortality (probably because product consumption is highly variable among individuals, products differ in fat content, and other confounding factors exist, such as the composition of the rest of the diet<sup>204–207</sup>). That said, the consumption of fermented dairy products (*i.e.*, cheese or yoghurt) is either uncorrelated,<sup>207</sup> or, more frequently, negatively correlated<sup>206,208,209</sup> with mortality. In studies involving populations with metabolic diseases or symptoms, FFs have not been found to have any adverse effects. At the same time, there has been no clear and compelling evidence that fermented dairy products have health benefits. Indeed, studies have arrived at conflicting results; the effects have been small or barely significant; the heterogeneity has been too dramatic to make apparent any significant interactions; or, lastly, too few studies have been performed to allow for any definitive conclusions. Consequently, slight beneficial effects appear to exist with regards to stroke risk (particularly for cheese consumption<sup>209–211</sup>), but there are no clear benefits in the context of cardiovascular diseases,<sup>212</sup> hypertension,<sup>212–214</sup> metabolic syndromes,<sup>182,212</sup> or weight management.<sup>205</sup> The only metabolic disease that seems to be positively affected by FF consumption is type 2 diabetes, where benefits might arise from the intake of yoghurt and, to a lesser extent, cheese.<sup>182,212,215,216</sup> No obvious patterns have been observed for other dairy products. The health benefits of yoghurts were recently highlighted by experts from the International Scientific Association for Probiotics and Prebiotics (ISAPP).<sup>4</sup> It is important to point out that fermentation in and of itself does not solely explain the above health benefits; the consumption of low-fat dairy products or the position of fats within complex matrices (such as those characteristic of yoghurts and cheeses) could also lead to the same positive outcomes.<sup>202</sup>

The consumption of fermented dairy products does not appear to influence the development of any cancers (*e.g.*, gastric, oesophageal, breast, pancreatic, ovarian, prostate, bladder, renal), or only a very slight effect exists.<sup>182,205,217</sup> The results for colon and colorectal cancer are not as consistent. The overall consumption of dairy products is generally associated with decreased risks, and there appears to be a dose–response effect;<sup>218–220</sup> however, such is not always true.<sup>221</sup> *meta*-Analyses and select literature reviews have highlighted that the fermentation process itself does not seem to have anticarcinogenic effects, even if cheese<sup>220</sup> and yoghurt<sup>221</sup> intake could have benefits in the case of colorectal cancers. However, there is an absence of any clear associations between fermented dairy products and several other cancer types.<sup>182,205,217,219</sup>

Lastly, research has also looked at the impact of fermented dairy products on GIT health (apart from cancer). First, there is no question that FFs help limit lactose intolerance. The consumption of yoghurt or fermented milks (such as kefir) is a recommended strategy for avoiding poor lactose digestion,<sup>182,205,222</sup> and yoghurt has an officially recognised

health claim: “live yoghurt cultures which can improve lactose digestion”.<sup>223</sup> Concerning transit regulation (*i.e.*, diarrhoea or constipation), the consumption of FFs seems to bring about improvements according to most, but not all, studies, an effect that has been linked to the presence of probiotics.<sup>192,205,224,225</sup> However, additional research is required to confirm the effects of fermented dairy products on transit-related gastrointestinal disorders, which is also true for the many other metabolic pathologies or symptoms mentioned above.

### 3.3. Other fermented products

The consumption of fermented or unfermented red meat at levels higher than the recommended daily threshold is linked to an increased risk of colorectal cancer, cardiovascular diseases, and diabetes.<sup>226–228</sup> There is debate surrounding the impacts of fermented alcoholic beverages (*e.g.*, beer, wine) on health conditions, including obesity, diabetes, cardiovascular diseases, and cancers;<sup>182</sup> the direction of the pattern is also highly dependent on the amount consumed.<sup>228</sup> For these two types of products, fermentation in itself is not necessarily the root cause of disease risk (*i.e.*, for red meat); whereas the fermentation product can also play a role (*i.e.*, the alcohol resulting from alcoholic fermentation).

Plant-based FFs represent the other main subject of study. Notably, extensive attention has been paid to the effects of fermented plant-based products such as coffee, cocoa, kombucha, cabbage-based products (*e.g.*, sauerkraut, kimchi), and soy-based products (*e.g.*, soy sauce, natto, tempeh, miso). In particular, soy-based FFs have been extensively studied and have generally been found to yield benefits,<sup>229</sup> including improved cardiovascular health, boosted anticarcinogenic activity, enhanced bone density, and greater cognitive function. Yet, it remains complex to disentangle the source of these effects: maybe they are associated with the protein and fibre contents of soy products or soy's levels of isoflavones (*i.e.*, genistein and daidzein).<sup>58</sup> Consequently, the health benefits attributed to natto, miso, or tempeh<sup>225</sup> could actually be the result of differences in baseline macro- and micronutrients in soybeans and not the fermentation process itself. In addition, there are few human studies looking at the actual health impacts of fermented soy-based products. Furthermore, most studies have been conducted in Asia,<sup>61</sup> which means that the results are not necessarily applicable at the global scale (as was true for research on dairy products). Still, these FFs do contain probiotic bacteria (namely LAB), which have recognised health benefits attributable to their bioactive metabolites.<sup>230</sup> Therefore, fermentation may have additional benefits *via* alterations in the gut microbiota;<sup>231</sup> this facet should be further investigated.<sup>59</sup> Finally, RCTs performed with soy-based FFs have largely been carried out on Asian populations. As in the case of fermented dairy products, future studies should take place within other populations.

When it comes to fermented cabbage-based products (sauerkraut in the USA and Europe; kimchi in Asia), several reviews have found such FFs to have broad health benefits (from relieving metabolic symptoms to displaying anticarcino-

genic activity<sup>186</sup>) or adverse effects (*e.g.*, provoking allergies or gut discomfort). That said, RCTs remain rare, and data for humans are too scarce to yield clear conclusions regarding specific health outcomes.<sup>225,232–234</sup> However, kimchi consumption is associated with an alteration in microbiota composition: kimchi-dominant species (including LAB and Bifidobacteria) are more abundant in the faeces of kimchi consumers.<sup>186,235</sup> As for soy-based products, there might be a positive effect of fibre content, antioxidant levels (attributable to the red peppers or garlic found in kimchi, for instance),<sup>225,236</sup> the high vitamin content of the raw materials, and the presence of probiotics. Yet, it is essential to test this hypothesis more objectively and scientifically *via* a larger number of well-designed RCTs.

For breads in general and sourdough breads in particular, fermentation appears to help lower FODMAP levels<sup>237</sup> and gluten content.<sup>238</sup> These ideas have been tested, and improvements in GIT health have been consistently seen across studies.<sup>225,237</sup> Still, further research is needed to explore the potential functions of the fermentation process in bread products and the quantitative importance of bread intake for populations consuming special diets. Notably, we must confirm the effects of bread products on gut health, food intolerances, and food allergies.

Lastly, several groups of fermented products are hypothesised to have health benefits, but fermentation is rarely mentioned as a potential driver. For instance, such is the case for chocolate in the context of metabolic syndromes and cardiometabolic health,<sup>239,240</sup> for coffee and its debated effects on cardiovascular diseases, obesity, and cancers (for details, see ref. 182), and for table olives, which might partially underlie the health benefits frequently attributed to the Mediterranean diet.<sup>241</sup> For these foods, the main drivers are often said to be levels of fibres, vitamins (vitamin E), mono- or polyunsaturated fatty acids, and phenolics (flavanols) (see part 2). Yet some of these compounds directly result from fermentation. For these food types, probiotic and postbiotic effects are rarely mentioned.

## 4. Conclusion

FFs have been part of our diets for millennia and have helped improve nutrition security. Indeed, fermentation is a relatively simple technique that helps preserve raw foods over long time periods, which was a boon before the development of cold storage and/or preservatives. In modern times, FFs are a major source of innovation and new consumer products within the food industry. Consequently, it is important to understand more about the functional and nutritional properties of FFs. To date, however, human studies, and *in vivo* animal research to a lesser extent, have failed to clearly demonstrate that FFs have the various health benefits that are frequently attributed to them. That said, there is general consensus regarding the beneficial effects of certain components associated with the fermentation process (*e.g.*, probiotic effects, metabolites, peptides, the degradation of harmful, antinutritional, or allergenic

compounds). Indeed, fermentation has clear advantages when it comes to degrading lactose or ANFs. There are health benefits for individuals who are lactose intolerant, and mineral absorption is notably improved for populations who eat plant-rich diets. In contrast, the picture painted is less clear for those with chronic metabolic pathologies. This discrepancy can be explained by the fact that it is difficult to accurately evaluate FF intake during longitudinal studies; it can be challenging to deal with confounding factors in experimental studies (and the choice of the control group is not always evident); and population responses to FFs can be highly variable (making it hard to select the health metrics to monitor). However, just because it is difficult to measure the health effects of FFs does not mean that they do not exist.

To more accurately ascertain whether FFs could have health benefits in the context of chronic metabolic diseases, it is essential to gather detailed information about the quantity and quality of FF consumption in populations. This approach requires closely monitoring the diets of study participants (*e.g.*, the FFs and other foods consumed) as well as characterising dietary ingredients (*e.g.*, macro- and micronutrient composition). It is only in this way that confounding factors can be dealt with. It is important to simultaneously thoroughly evaluate health outcomes using an appropriate (and, if possible, wide range) of various metrics with a view to accurately and precisely capturing variation in health status. From this foundation, two strategies can be adopted. First, the impact of FF consumption overall can be studied in a target population. For example, comparisons could be carried out between individuals who consume large *versus* small quantities of FFs (*e.g.*, an observational study, as has already been performed in a healthy population<sup>199</sup>) or between groups consuming diets with differing FF levels (*e.g.*, a longitudinal experimental study). Such research would help inform future population-level recommendations related to FF intake. Second, it is important to take a more mechanistic approach, whereby the effects of a single FF are tested. This strategy has already been utilised in past research. However, as noted before, it is crucial for future studies to give more thought to control group choice, which is necessary if we wish to perform reliable comparisons of health effects. For example, the research question and its implicit comparison of interest must be more clearly delineated so that it is evident which aspect of FFs is under consideration (*e.g.*, FF composition, matrix effects, metabolite production, microorganism identity).

## Author contributions

Writing – original draft: FR, ISA; writing – review & editing: all authors.

## Conflicts of interest

The authors declare no conflicts of interest.

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