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FODMAP modulation as a dietary therapy for IBS: Scientific and market perspective

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Abstract

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) is a promising therapeutic approach to reduce gastrointestinal symptoms associated with irritable bowel syndrome (IBS). However, a shift toward a more sustainable, healthy diet with higher inclusion of whole-grain cereals (i.e., wheat, rye, barley) and pulses, naturally rich in FODMAPs, poses a severe challenge for susceptible individuals. Dietary restriction of fermentable carbohydrates (commonly called the "low FODMAP diet") has received significant consideration. Hence, the development of functional low FODMAP products is emerging in food science and the food industry. In this review, we evaluate the most promising yet neglected (bio)-technological strategies adopted for modulating the FODMAP contents in complex food systems and the extent of their uptake in the global food market. We extensively investigated the global low FODMAP market, contrasted with the status quo in food science and discussed the key principles and concomitant challenges of targeted FODMAP reduction strategies. Powerful tools are available which are based either on the use of ingredients where FODMAPs have been physically removed (e.g., by membrane filtration) or biotechnologically reduced during the food processing, mediated by added enzymes, microbial enzymes during a fermentation process, and seed endogenous enzymes. However, <10% of the small market of functional products with a low FODMAP claim (total ~800 products) used any of the targeted FODMAP reduction techniques. The global market is currently dominated by gluten-free products, which are naturally low in FODMAPs and characterized by inferior sensory attributes.

Abbreviations: dm, dry matter; DP, degree of polymerization; EPS, exopolysaccharides; FBD, functional bowel disorders; FGID, functional gastrointestinal disorders; FLAB, fructophilic lactic acid bacteria; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; FP, fagopyritols; GOS, α-galactooligosaccharides; HPAEC-PAD, high performance anion exchange chromatography coupled with pulsed amperometric detection; HPLC-ELSD, high performance liquid chromatography coupled with evaporative light-scattering detecion ; IBS, irritable bowel syndrome; LAB, lactic acid bacteria; LF, low FODMAP; LFD, low FODMAP diet; PHGG, partially hydrolyzed guar gum; RFO, raffinose family oligosaccharides; XOS, xylo-oligosaccharides.

KEYWORDS
gluten-free, yeast, sourdough, enzymes, germination

1 | INTRODUCTION

Poorly absorbed, osmotically active, and rapidly fermentable carbohydrates comprised under the acronym FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) have increasingly gained attention in both scientific literature and the global food market in the last few years. This is due to the finding that the ingestion of FODMAPs by individuals with functional gastrointestinal disorders (FGIDs), particularly irritable bowel syndrome (IBS), was associated with the onset of severe and painful gastrointestinal symptoms (Gibson & Shepherd, 2005, 2010). The commonly cited list of FODMAPs includes fructans, α-galactooligosaccharides (GOS), lactose, fructose in excess of glucose, and polyols, but is not limited to these. The identification of other dietary carbohydrates with similar physiological effects may extend this list (Gibson et al., 2020; Halmos & Gibson, 2019). FODMAPs are quite ubiquitous dietary carbohydrates, which are not digested in the human small intestine, and delivered to the large intestine, where they are readily fermentable by the colonic bacteria. Also, especially poorly absorbed monosaccharides and polyols are small and osmotically active molecules driving large amounts of water into the intestinal lumen. While these physiological mechanisms do also occur in healthy individuals, in susceptible individuals they induce unpleasant and painful gastrointestinal symptoms, such as an altered bowel movement, abdominal pain, or excess flatus (Gibson & Shepherd, 2005, 2010; Gibson et al., 2007; Lenhart & Chey, 2017). It was shown that the avoidance of FODMAPs as a dietary therapy, the low FODMAP diet (LFD, cf. Figure 1), is a successful therapeutic approach to alleviate symptoms in >70% of IBS patients (Halmos et al., 2014). Palsson et al. (2020) recently re-evaluated the prevalence of functional bowel disorders (FBDs, subtype of FGIDs, all characterized by various severe gastrointestinal symptoms and substantially impaired quality of life). They found that >25% of the adult population in the United States, Canada, and the United Kingdom suffers from FBDs, of which ~5% was identified as IBS. While IBS and other FBD are more prevalent in women than in men, the overall prevalence seems to be decreasing after mid-life (older than 50 years) (Palsson et al., 2020). A recent global study (evaluated the prevalence of FGIDs based on surveys in 33 countries) demonstrated that IBS is in fact a worldwide spread disorder (Sperber et al., 2021).

Despite the solid scientific evidence that the LFD can effectively reduce symptoms in IBS patients, the diet is also facing criticism, particularly regarding avoiding healthy dietary fibers (Brouns et al., 2019; Halmos & Gibson, 2019). It is crucial that the LFD is well known to the medical sector and dieticians, who should fully support and lead the correct protocol of the diet (restriction phase > reintroduction phase > personalized LFD, cf. Figure 1) as a dietary therapy for IBS (Halmos & Gibson, 2019; Whelan et al., 2018). The LFD does not mean a complete avoidance of any fermentable dietary fiber, but solely those that are easily fermented and lead to gastrointestinal symptoms in individuals with a pronounced sensitivity toward those. The same principle applies to the low FODMAP product development. Atzler et al. (2021a) recently reviewed and identified characteristics of dietary fibers suitable for an LFD (e.g., low fermentation rate, low osmotic activity). Indeed, a key principle of the LFD is the replacement of nontolerated high FODMAP foods with nutritionally equivalent low FODMAP foods (Figure 1). In this matter, the availability of appealing, high quality, and nutritious functional low FODMAP products to facilitate the food choice of IBS patients in the replacement of the conventional high FODMAP products is essential (Figure 1). Particularly whole grain cereals, pulses, and products made from those are a substantial source of energy, dietary fiber, and micronutrients in a healthy and sustainable plant-centered diet; solely wheat and wheat-based products account for one fourth of the daily calorie intake in the European population (FAOSTAT, 2021). However, due to naturally occurring FODMAPs in cereals such as wheat or rye, and pulses (i.e., fructans and GOS), products made from those have to be largely avoided by IBS patients (Biesiekierski et al., 2011; Ispiryan et al., 2020; Muir et al., 2019). Besides fructans and GOS, other FODMAPs mostly found in dairy (lactose), and various fruit, vegetables, and fermented foods (fructose in excess to glucose, polyols, melibiose) can be found in cereal- and pulse-based products, derived from other ingredients or the processing (Ispiryan et al., 2020). The following FODMAP cutoff levels were validated and established based on the findings of clinical studies: per serving of food <0.3 g of oligosaccharides, for example, sum of fructans and GOS in pulses and core grain-products; <0.15 g of excess fructose; <0.4 g of polyols; <1 g of lactose; <0.5 g total FODMAPs excluding lactose (Barrett et al., 2010; Halmos et al., 2014; Ong et al., 2010; Varney et al., 2017). These should be the benchmark for the targeted low FODMAP product development. Several studies investigated FODMAP reduction strategies, including the use of low FODMAP ingredients, and

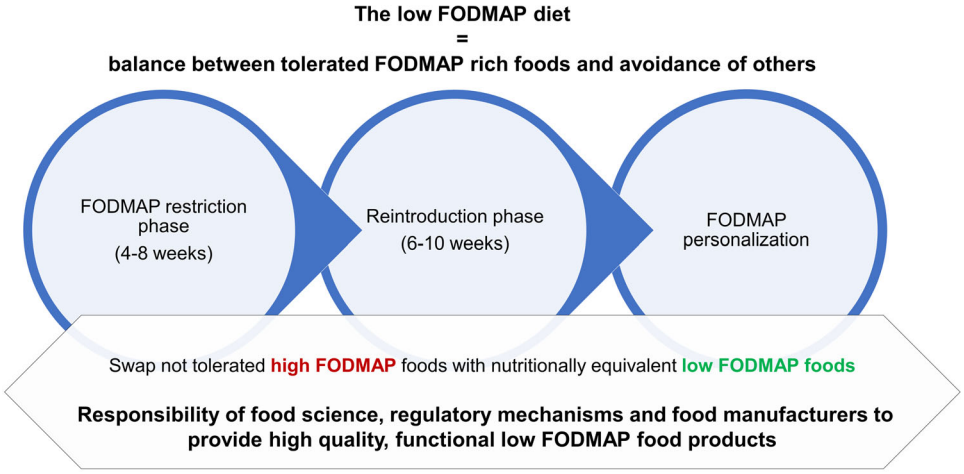

FIGURE 1 Low fermentable oligosaccharides, disaccharides, monosaccharides, and polyol (FODMAP) diet and importance of nutritious functional low FODMAP products

biotechnological FODMAP degradation through the action of purified enzymes, microbial enzymes during fermentation (specific yeast and lactic acid bacteria [LAB]), and activation of seed-endogenous enzymes during germination (Atzler et al., 2020, 2021b; Fraberger et al., 2018; Ispiryan, Kuktaite, et al., 2021; Li et al., 2020; Longin et al., 2020; Loponen & Gänzle, 2018; Loponen et al., 2017; Schmidt & Sciurba, 2021; Struyf, Laurent, Verspreet, et al., 2017; Ziegler et al., 2016). The fundamental key principles of biotechnological FODMAP reduction have been recently reviewed by Nyyssölä et al. (2020).

Ultimately, this review aims to systematically reveal and interconnect the current state of knowledge of the most effective and applicable targeted FODMAP reduction strategies in scientific literature and their actual application to produce functional low FODMAP products on the global market, with a focus on bakery products and pasta. It is shown which market segments may be sufficiently covered and where currently known technologies should be more applied, while concomitant limitations are highlighted. Furthermore, the importance of a targeted approach for producing low FODMAP products is demonstrated, whether for products based on primarily low FODMAP ingredients or for biotechnological FODMAP reduction strategies.

2 | GLOBAL MARKET ON FUNCTIONAL LOW FODMAP PRODUCTS

The availability of functional low FODMAP food products on the global market was systematically assessed for this review (until April 19, 2021). All food products, recipe developers, and ingredients certified by the two Australian programs, the "Monash University Low FODMAP Certification Program" and the "FODMAP Friendly Program" were included in the global market analysis. Both programs certify foods according to the FODMAP cutoff values per serving of food and list the certified products in their mobile phone applications or websites (https://www.monashfodmap.com/; https://fodmapfriendly.com/). Furthermore, products, which the manufacturer claimed to be suitable for an LFD, were included in the analysis. Regardless of the wording of certifying organization or the manufacturers' FODMAP claim, all products included in the study are referred to as low FODMAP products (LF products). Products that were presented in specialized online shops (e.g., fodmarket.co.uk, fodshopper.com.au, foodoase.de) as suitable for an LFD, but were neither analytically tested by the two certification programs nor had a manufacturer's claim, were not included.

The analysis resulted in 791 products with a FODMAP related claim, available on the global market. Thereof, 97% were certified by either of the two Australian certification programs. Furthermore, 18 products (2%) were found, which were claimed by the manufacturer to be low in FODMAPs or suitable for an LFD. Nine products (1%) which were claimed to be based on a "low FODMAP wheat" were included in the overall figure of available products (Figure 2, products with FODMAP claim) but were excluded from further evaluations, as a low FODMAP content of the actual products was not stated and potentially not given.

Since the introduction of the two certification programs in 2013/2014 (Lederman, 2014), an increasing number of food manufacturers joined the programs, with 127 companies offering their range of certified functional low FODMAP products today (Figure 2, companies certified from 2013 to 2021). Corresponding to the origin of the FODMAP concept, founded in 2005 by the research

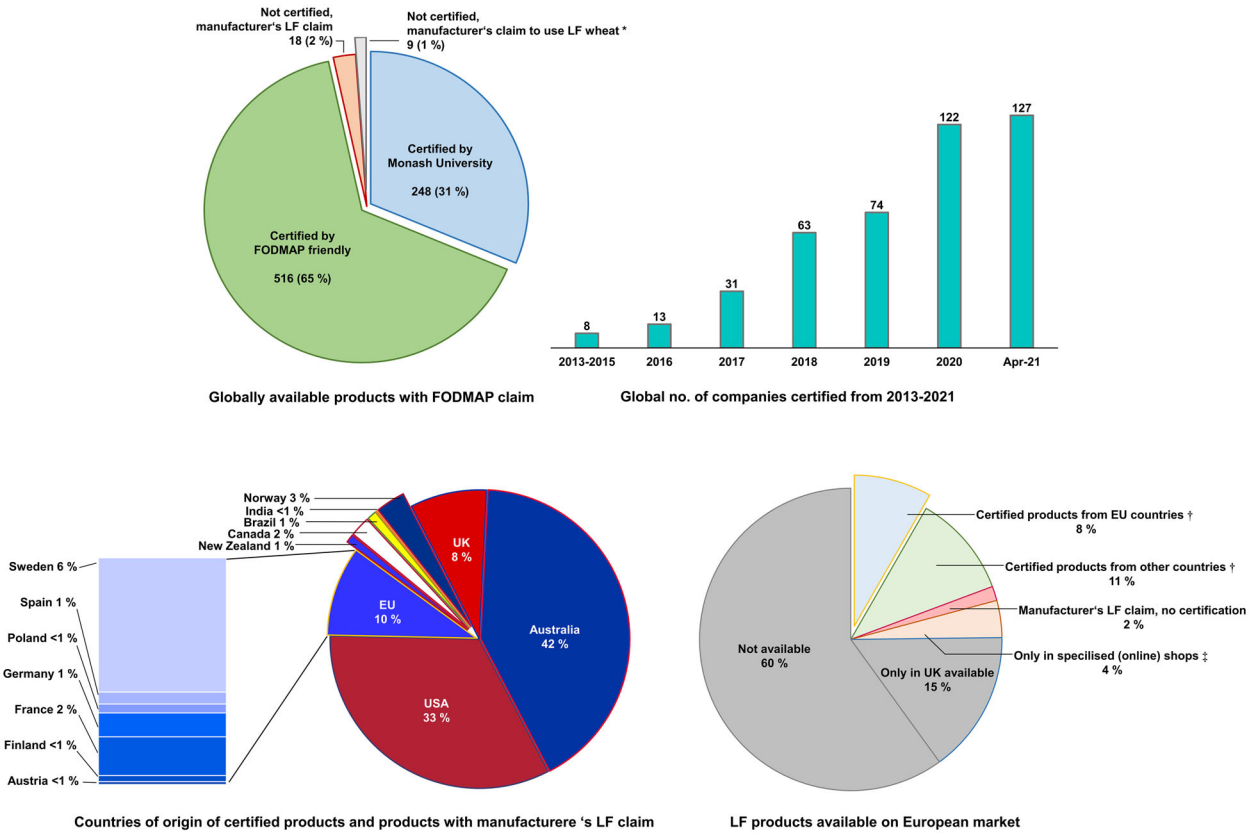

FIGURE 2 Globally available products with fermentable oligosaccharides, disaccharides, monosaccharides, and polyol (FODMAP) claim: *not certified products with manufacturer's claim to use low FODMAP wheat as ingredient (2ab wheat) are not included into further evaluations as those products are not necessarily low FODMAP. Products available on European market: †from all certified products from European Union (EU)-based manufacturers, and certified products from other than EU-countries, which are also commonly available on EU market >90% do not seem to carry the certification label on the product packaging. ‡Specialized online shops such as foodoase.de or specific local health food stores offer imported, certified products, for example, from Australia

group of Prof. Peter Gibson (Gastroenterology Department, Monash University Australia) (Gibson & Shepherd, 2005) and the certification programs, the majority of the certified products (42%) were from Australian food manufacturers. Products originating from the United States accounted for 33% of all low FODMAP products. With 8%, the United Kingdom had the third most significant share of LF products on the global market. The remaining 17% were from few European Union (EU) countries (Sweden, Spain, Poland, Germany, France, Finland, Austria), and Norway, India, Brazil, Canada, and New Zealand.

2.1 | Lack of products on European market and legal situation

While 60% of the certified products were not at all available on the European market (Figure 2, availability of LF products in Europe), 21% were only available in the United Kingdom in specialized shops or had no certification (only manufacturer's FODMAP claim). Only 19% of all functional LF products were commonly available in EU countries, while >90% of these did not actually carry any FODMAP related statement or claim (e.g., certification logo) on the packaging. In Australia, the FODMAP concept is recognized in the Australian Food Standards Australia New Zealand (FSANZ) with a definition of carbohydrates belonging to the umbrella term and the scientific evidence on physiological effects (FSANZ). Both Australian programs test food products in accordance with FSANZ guidelines (regarding food sampling procedures and accredited laboratories) and certify products. The Australian (as well as US) legislation allows for the endorsement/certification of food products by experts provided that the product complies with the respective requirements (i.e., cutoff levels defined in programs' certification criteria) (16 CFR § 255.3; Méance et al., 2017). However, such expert testing/certification programs to date only exist in Australia, with their testing laboratories in Australia and the United States (Monash University, 2021). For food

manufacturers in the European Union to label products safely and distinctly as a product with a low FODMAP content, a definition of the term and the necessary criteria, such as an EFSA approved nutrition claim (Regulation (EC) No. 1924/2006; Regulation (EU) No. 1169/2011) is entirely missing. A precise specification of the low FODMAP criteria, applied for low FODMAP certifications in Australia, must be incorporated in the EU food regulations, such as it already exists for gluten-free or gluten-reduced foods (Commission implementing regulation (EU) No. 828/2014; Regulation (EU) No. 1169/2011). Also, the introduction of standardized adequate analytical methods for an accurate quantification of all FODMAPs in different food matrices is needed. Therefore, a clear definition of target analytes and minimal required detection levels is essential. While polyols, mono-, disaccharides, and GOS are commonly accurately quantified via HPLC-ELSD (high performance liquid chromatography coupled with evaporative light-scattering detection) (Muir et al., 2009) or HPAEC-PAD (high performance anion-exchange chromatography coupled with pulsed amperometric detection) (Ispiryan et al., 2019) using authentic reference standards, the choice of an appropriate technique for the quantification of fructans deserves careful consideration, as discussed in Section 4. The establishment of the necessary regulatory framework would increase the legal clarity for food manufacturers and consumers while ensuring the correct application of the low FODMAP criteria and allow for a facilitated food choice for individuals adhering to the LFD.

Finally, the lack of regulations also comes with an increased risk of false information patients may receive from food producers or nonscientific articles, limiting the potential success of a correctly conducted LFD. In this context, the standard classification of a product's FODMAP content solely based on the list of ingredients may not always be accurate. The following factors strongly limit the correctness of such classification: (1) The food production process may alter the FODMAP profile in an unknown manner, for example, yeast or sourdough fermentation or the use of a specific type of wheat such as spelt does not guarantee a low FODMAP content. (2) The product may contain technical additives which are not listed in the ingredients but influence the FODMAP profile, for example, enzymes that are added as processing aids may alter the carbohydrate profile of the product (release high levels of poorly absorbed monosaccharides). (3) The FODMAP contents of ingredients may vary substantially and not allow for an estimation of the product's FODMAP content. For instance, protein ingredients from pulses or sprouted grain material can have highly variable FODMAP contents (Ispiryan et al., 2020; Ispiryan, Kuktaite, et al., 2021; Joehnke et al., 2021; Tuck et al., 2018; Vogelsang-O'Dwyer, Petersen, et al., 2020), which are not predictable unless detailed information on the production process of the ingredient was provided, or the contents were analytically tested. Hence, to allow for food producers to exploit the scientifically proven approaches for low FODMAP food production, shown in the following sections, clear regulations defining the clinically tested cutoff levels and suitable analytical techniques for the FODMAP quantification are necessary.

2.2 | Categories of available functional low FODMAP products

Among all products with an LF claim (certification or manufacturer's claim), 70 products (9%) were breads, rolls, bagels, and wraps. Furthermore, six pizza bases (1%), 24 pasta products (3%), 24 baking mixes (3%), 73 breakfast cereals (9%), 135 sweet snacks, muesli bars, and pastry products (17%), 75 savory snacks and crisp breads (10%), 21 dairy alternative products (3%), and one beer were certified as LF products. Also 44 ingredients (6%) had an LF claim (Figure 3). These cereal-, pulse-, nut-, and seed-based products and ingredients comprised 60% of all products with an LF claim and will be further discussed concerning their "FODMAP reduction" approaches and their base ingredients or the types of ingredients. Furthermore, 23% of the certified products were seasonings, sauces, and condiments. The remaining 17% were distributed between dairy products, fermented vegetables, meat and fish, ready to eat meals, tea, dietary supplements, food for special medical purposes, fruit (kiwifruit), and three meal delivery services.

2.3 | Abundance of gluten-free products

Ingredients from gluten-free products also often have a low FODMAP content (Ispiryan et al., 2020). Unsurprisingly, >80% of the cereal-, pulse-, nut-, and seed-based products and ingredients were also gluten-free (the majority of which were rather previously existing products than produced as targeted functional LF product) (Figure 3). Correspondingly, sweet and savory snacks, muesli bars, pastry, crisp breads, baking mixes, breakfast cereals, dairy alternative products, and the beer were all solely based on gluten-free ingredients or nongluten-free oat (8% of the breakfast cereals contained low amounts of barley malt extract and were thus not gluten-free, Figure 3).

From the breads, rolls, bagels, and wraps, 33 products were based on gluten-free flours or flour composites (e.g., rice flour, maize-, tapioca-, potato starch). Pulse flours, such as soy flour, are also often found in gluten-free formulations, but with very low addition levels; hence, their

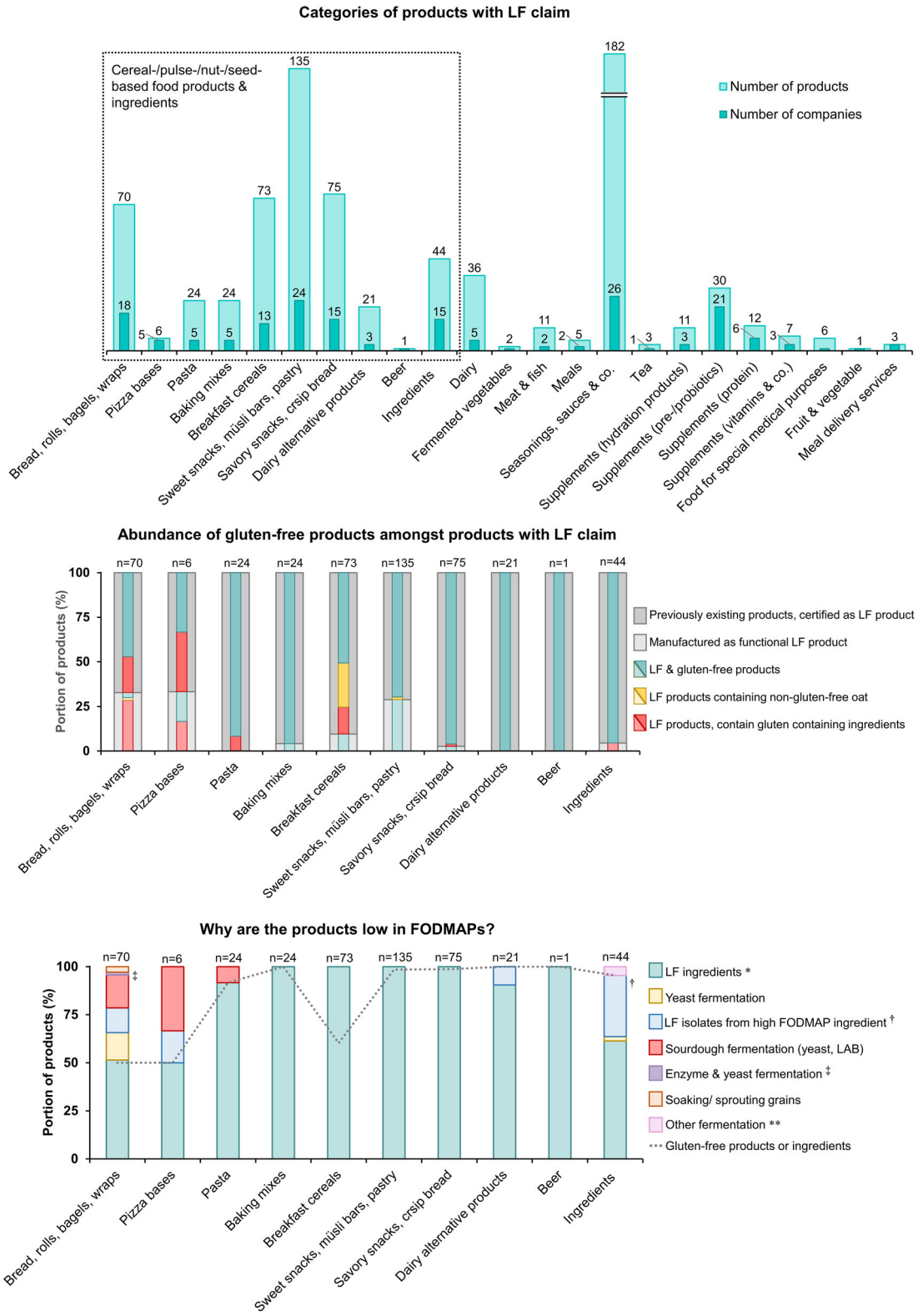

FIGURE 3 Categories of products with low fermentable oligosaccharides, disaccharides, monosaccharides, and polyol (FODMAP) claim, abundance of gluten-free products among those and underlying FODMAP reduction technique. *Products or ingredients, based on solely low FODMAP ingredients, contain only low levels of high FODMAP ingredients/high FODMAP ingredients with a very low serving size. †Gluten and starch-based ingredient from LO-FO pantry, based on patented technology (Pearce & Barrie, 2015). ‡Bread from Fazer based on patented FODMAP reduction technology with LOFO enzyme ingredient (Loponen et al., 2017). **Cocoa bean fermentation; includes different yeast, lactic acid bacteria, and acetic acid bacteria that ferment α-galactooligosaccharides (GOS) (Megías-Pérez et al., 2018; Schwan & Wheals, 2004)

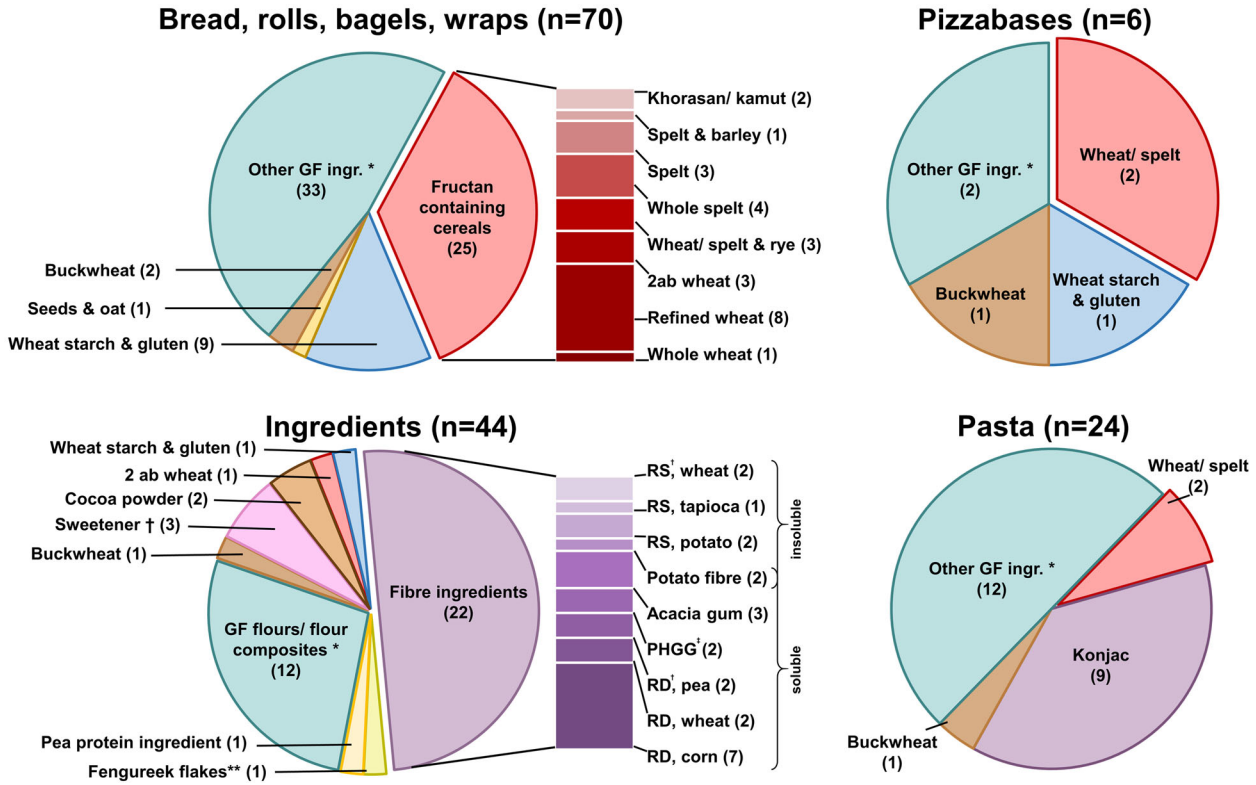

FIGURE 4 Base ingredients of low fermentable oligosaccharides, disaccharides, monosaccharides, and polyol (FODMAP) bread, rolls, bagels, wraps, pizza bases, pasta, and types of raw ingredients with low FODMAP claim. *Gluten-free (GF) flours and flour composites include rice flour, maize and potato flour/starch, tapioca starch, and quinoa flour. †RS, resistant starch; RD, resistant dextrin; ‡PHGG, partially hydrolyzed guar gum. **Fenugreek seeds are legume seeds and accumulate α-galactooligosaccharides (GOS) (Campbell & Reid, 1982), and low FODMAP certification is for a small serving of 20 g

impact on the FODMAP contents is irrelevant. Similarly, two of the six pizza bases, 12 pasta products, and 12 ingredients were based on gluten-free flours or flour composites (Figure 4). Furthermore, two wraps, one pizza base, one pasta product, and one ingredient were based on buckwheat. However, despite its high nutritional value and general health benefits (Wijngaard & Arendt, 2006), the classification of buckwheat as low FODMAP grain may be debatable as previously discussed (Ispiryan et al., 2020; Ispiryan, Kuktaite, et al., 2021). Buckwheat contains nondigestible, fermentable carbohydrates, namely fagopyritols, with 0.2%–3% found in the groats' milling fractions (Steadman et al., 2000). These compounds have similar structural and biochemical properties to GOS and are suspected to have a similar effect on IBS patients. With the cutoff level for oligosaccharides in core grains being 0.3 g per serving, fagopyritol concentrations in buckwheat may be sufficient to trigger IBS symptoms. However, to our knowledge, no clinical studies are available on the tolerability of buckwheat by IBS patients; the IBS-symptom induction by buckwheat should be further investigated and the necessity of an inclusion of fagopyritols into routinely analyzed FODMAPs elucidated.

3 | STRATEGIES TO PRODUCE LOW FODMAP PRODUCTS AND THEIR CURRENT APPLICATION

Low FODMAP products can be either produced by avoiding high proportions of high FODMAP ingredients in the product formulations or through biotechnological tools to degrade FODMAPs during the production process (Table 1, Figure 5). Regardless the approach used, the choice of ingredients should ensure that products are, as far as possible, rich in vitamins, minerals, complex non-FODMAP carbohydrates, and protein to enable the replacement of conventional FODMAP rich food products with low FODMAP alternatives of equal or greater nutritional and sensory quality. Targeted FODMAP reduction techniques are particularly relevant for bakery products, pasta, and their ingredients. This agrees with the unexploited potential of the current market situation and the prognosis for a high growth opportunity seen for the still "science-based niche" of low FODMAP bakery products (Mellentin, 2020). In this section, for each approach, the state of knowledge of the principle, the challenges, the current application on the market, and potential associated patents are shown.

TABLE 1 Summary of studied targeted fermentable oligosaccharides, disaccharides, monosaccharides, and polyol (FODMAP) reduction approaches in ingredients and products and current application on the global market

Approach [references]	Products/ingredients studied	FODMAPs reduced	Mechanism of FODMAP removal	Application on current market[a]
		Physical FODMAP removal		
LF ingredients isolated from high FODMAP material [1–6]	Bread or ingredient based on starch and vital gluten from wheat	Fructans	Fractionation of high FODMAP ingredient (starch, protein, fiber) and removal of FODMAPs as supernatant from isoelectric point precipitates from proteins or via aqueous washing and membrane filtration techniques	One "plain flour," 10 products: breads, rolls, pizza base; four fiber ingredients
	Protein ingredients (lentils, fababean, lupin), plant-based milk alternative	GOS		Two dairy alternative plant drinks, one protein ingredient, seven fiber ingredients
Cooking [7–11]	Pasta (durum wheat semolina)	Fructans	Soluble carbohydrates leach into cooking water	–
	Various pulses	GOS		
		Biotechnological FODMAP reduction during processing		
Enzyme addition (combined with fermentation) [12–15]	Wheat and rye breads	Fructan/excess fructose/mannitol	Added exo-inulinase FruA from *L. crispatus*, or invertase from *Aspergillus niger* combined with baker's yeast or *L. reuteri* or *L. frumenti* or *A. kunkeei* or *F. fructosus* fermentation: synergistically hydrolyze fructans, baker's yeast and/or LAB metabolize excess fructose and mannitol	One whole wheat-based bread
	Yellow pea protein-based crackers, meat analogue, spoonable product	GOS	Added commercial and recombinantly produced α-galactosidases from *Neosartorya fisherii* degrade GOS to sucrose and galactose	–
Yeast-fermentation (combined with enzyme addition) [14, 16–25]	Whole and refined wheat (different varieties) bread	Fructan, excess fructose	Yeast-invertase and/or inulinase (*S. cerevisiae, K. marxianus, L. fermentati)* mediated hydrolysis of fructans, yeast metabolizes excess fructose	10 breads made from predominantly refined flours
	Whole wheat and whole wheat - whole rye breads	Excess fructose	Baker's yeast metabolizes excess fructose resulting from raffinose/sucrose/fructan-hydrolysis by LAB mediated or added inulinases	One whole wheat-based bread
	Ingredient (ancient wheat flour, *Triticum turgidum* forma *sanus*)	fructan, excess fructose	Yeast-mediated (species unknown) enzymes invertase and/or inulinase hydrolyze fructans and yeast metabolizes excess fructose	One ingredient: "2ab wheat flour"
LAB sourdough fermentation (combined with enzyme addition) [12–14, 21, 26–28]	Whole wheat, refined wheat, whole wheat - whole rye breads	Fructan, excess fructose	Exo-inulinase expressing LAB (FruA: *L. crispatus*; FosE: *L. paracasei*) hydrolyze fructans; LAB and yeast metabolize excess fructose without mannitol production	-

(Continues)

TABLE 1 (Continued)

Approach [references]	Products/ingredients studied	FODMAPs reduced	Mechanism of FODMAP removal	Application on current market[a]
	Refined wheat bread	Excess fructose, mannitol	Strictly fructophilic lactic acid bacteria (FLAB; *A. kunkeei* or *F. fructosus*) efficiently metabolize excess fructose resulting from raffinose/sucrose/fructan-hydrolysis by added invertases and mannitol produced from fructose	–
		Fructan, excess fructose	Conventional sourdough cultures (*L. plantarum*, *L. citreum*, *F. sanfranciscensis*, *L. fermentum,* etc.) synergistically with baker's yeast and other sourdough yeast (*C. milleri*) hydrolyze fructans and reduce excess fructose levels without production of high mannitol levels	16 products made from predominantly refined flours: breads, bagel, pasta, pizza base
Germination/ sprouting/ malting [11, 29]	Fresh sprouts (lentils, mung beans, buckwheat); malted ingredients (lentils, chickpeas, buckwheat)	GOS, FP[b]	Activation of endogenous α-galactosidases during germination, hydrolyze GOS; released galactose is utilized by growing embryo	–
Sprouting [11]	Fresh sprouts (rye, barley, wheat)	fructan	Dilution of present fructans in grains due to soaking with water; activation of endogenous fructan hydrolases during germination not reported[c]	Two breads from sprouted spelt and kamut

Abbreviations: GOS, α-galactooligosaccharides; LF, low FODMAP; LAB, lactic acid bacteria.

[a]Only products claimed to be low FODMAP by manufacturers or products certified by FODMAP friendly or Monash University.

[b]Fagopyritols (FP) are major fraction of soluble carbohydrates of buckwheat, indigestible, and suspected to act as FODMAP.

[c]Apparent impact of sprouting contradicts different reports (Cozzolino et al., 2016; Ispiryan et al., 2021b; Krahl et al., 2008; MacWilliam et al., 1956) on impact of malting causing fructan accumulation throughout germination phase; potential shift fructan metabolism with alterations in germination conditions not yet studied.

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3.1 | Avoidance of high FODMAP ingredients—Use of ingredients naturally low in FODMAPs

Ingredients, that mainly contribute to high FODMAP contents of conventional products are typically fructan accumulating cereals, including all types of wheat (e.g., bread wheat, spelt, emmer, kamut), rye and barley, and GOS accumulating pulses (e.g., soy, lentils, lupin) (Gélinas et al., 2016; Ispiryan et al., 2020). Fructan levels between 1% and 5% have been reported in different cereals, with a substantial part being stored in outer grain layers (Haskå et al., 2008; Ispiryan et al., 2020). Hence, products made from wholegrain flours contain high FODMAP levels (Biesiekierski et al., 2011; Ispiryan et al., 2020; Varney et al., 2017). Pulses accumulate GOS (raffinose, stachyose, verbascose, ajugose; predominantly stachyose) at levels from 1% up to >10% (Ispiryan et al., 2020; Martínez-Villaluenga et al., 2008). In contrast, ingredients naturally low in FODMAPs comprise different flours and starches from gluten-free cereals, pseudo cereals, or vegetables that do not accumulate fructans, GOS, or other FODMAPs

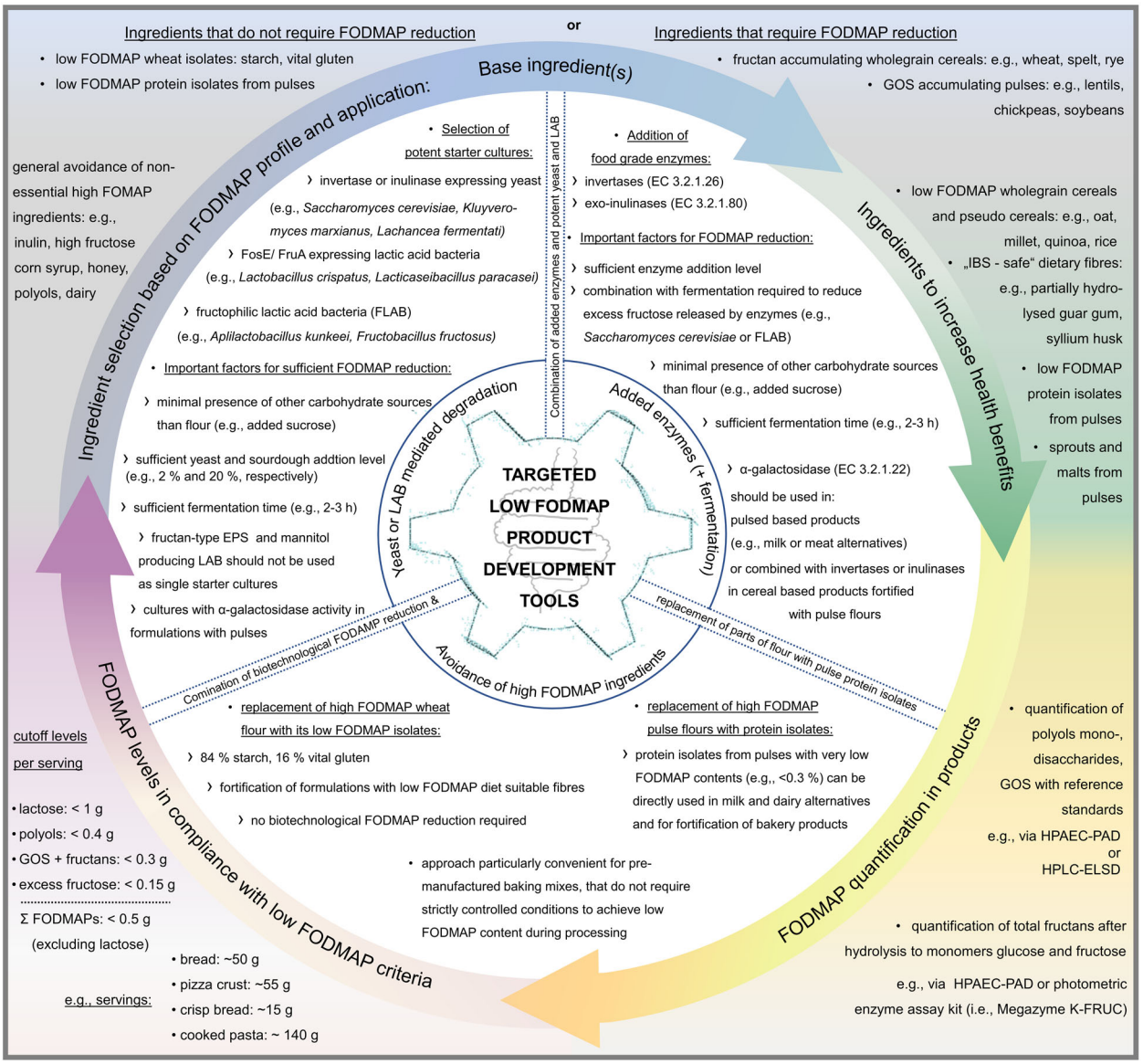

FIGURE 5 Targeted low fermentable oligosaccharides, disaccharides, monosaccharides, and polyol (FODMAP) products development strategies suitable for cereal- and pulse-based bakery products, pasta, and beverages

(e.g., oat, millet, rice, maize, quinoa, potato) (Ispiryan et al., 2020). Hence, if the formulation of gluten-free products does not contain high amounts of other FODMAP-rich ingredients (e.g., dairy as a source of lactose, high fructose corn syrup, honey, polyol sweeteners) those are often found to also be very low in FODMAPs (Biesiekierski et al., 2011; Ispiryan et al., 2020).

As shown in the previous section, >80% of the commercially available products and ingredients with an LF claim were based on naturally low FODMAP and gluten-free ingredients (Figures 3 and 4). Consequently, gluten-free products, also certified as low FODMAP, currently dominate the small market of functional low FODMAP products. However, gluten as an essential functional component does not have to be eliminated from the ingredients. Thus, the research of more targeted approaches has been of great interest and revealed the potential of different methods (Table 1, Figure 5).

Among the LF certified ingredients, there were also three different sweeteners, based on allulose, stevia and thaumatin, and erythritol, respectively. The latter is a polyol, and even though it is known that erythritol does not cause the same effect in healthy individuals as other polyols (better absorbed and less fermented by gut bacteria), its effect on IBS patients was not investigated (Arrigoni et al., 2005; Lenhart & Chey, 2017). While the Monash University certification criteria state that foods with added FODMAPs, among which erythritol is included, are not even eligible for certification, an erythritol-based sweetener is certified by the second certification program

(FODMAP friendly). Such discrepancies underline the urgency of a clearly defined FODMAP concept incorporated in the respective legal framework. Finally, in the context of alternative non-FODMAP sweeteners, the chocolate manufacturer Cavalier holds a patent on the production of low sugar/sugar-free products sweetened with the sucrose/glucose/polyol alternatives mogroside-enriched monk fruit extract, isomaltulose or the sweet tasting proteins thaumatin, monellin, mabinlin, pentadin, brazzein, curculin, or miraculin (Table 2) (Vergedem, 2016).

3.2 | Use of low FODMAP ingredients, isolated from high FODMAP material

Protein and starch isolates or fractions from high FODMAP raw material, such as wheat or pulses, can have significantly lower fructan or GOS contents in the obtained functional ingredients, depending on their production process. Such ingredients may serve as base ingredients in different LF product formulations, which do not require any further FODMAP reduction techniques during the food processing (Figure 5).

Joehnke et al. (2021) demonstrated that the isolation of lentil protein by ultrafiltration was highly effective in removing compounds with a molecular weight below 10 kDa (this includes GOS), resulting in an ingredient with only ~0.4% GOS obtained from lentils with ~4% GOS. They also reported that the isolation of a protein ingredient from the same raw material, using isoelectric point precipitation, resulted in ~2% residual GOS in the ingredient. In contrast, slightly different isoelectric point precipitation processes for the isolation of fababean and lupin protein ingredients have been shown to also remove most native GOS (maximum 0.1% of residual GOS) effectively (Vogelsang-O'Dwyer, Petersen, et al., 2020; Vogelsang-O'Dwyer, Bez, et al., 2020). However, not all types of protein ingredients may be suitable in LF formulations without additional FODMAP reduction during the processing of the product. Several commercial pulse protein ingredients and a fababean protein-rich ingredient obtained by dry fractionation were shown to contain comparable GOS levels such as native pulses (~5%–11%) (Ispiryan et al., 2020; Vogelsang-O'Dwyer, Petersen, et al., 2020). Pulse protein ingredients with low FODMAP contents could serve as base ingredients in dairy alternative products, as it was recently shown for milk alternatives based on lupin protein isolates (Vogelsang-O'Dwyer et al., 2021). Among the commercial LF products, two soy protein-based milk alternatives and a pea protein ingredient were available (Figures 3 and 4). The use of pulse protein ingredients in milk alternatives does not only serve the LFD. Due to environmental-, ethical-, and health-related concerns of consumers the demand for plant-based dairy alternatives is generally increasing.

For the production of LF bakery products, the replacement of wheat flour with its isolates, which are essential to the baking process, wheat starch and vital gluten, supplemented with non-FODMAP fibers, is an elementary yet beneficial, broadly applicable and reliable approach. The wheat isolates were reported to contain only a fraction of the wheat-derived fructans (traces in starch and ~0.6% in vital gluten) (Ispiryan et al., 2020). Hence, an 84% starch- and 16% gluten-based formulation (according to the composition of wheat) would only account for ~0.1% wheat-derived fructans, in contrast to ~2% fructans from whole wheat flour. Atzler et al. (2021b) applied this approach and investigated the potential enrichment of such starch- and gluten-based LF bread formulations with supposedly non-FODMAP, soluble (guar gum, psyllium) and insoluble fibers (bamboo, cellulose) at concentrations of the EU nutrition claims "source of fiber" (3%) and "high in fiber" (6%) (Regulation (EC) No. 1924/2006). They evaluated the consequences of incorporating fibers on technological and nutritional bread quality characteristics and highlighted the benefits of the LF bread fortification with psyllium at 3%. The complete or partial replacement of wheat flour with its functional isolates is currently applied in several commercially available LF products, including bread, rolls, a pizza base, and an ingredient (Figures 3 and 4). The latter is a reconstituted wheat "plain flour," made from wheat starch, vital gluten, and guar gum. Pearce and Barrie (2015) (Shoalhaven starches PTY. Ltd; product marketed as LO-FO pantry) patented their technology to produce low FODMAP wheat isolates, including extensive aqueous washing and membrane filtration steps to effectively remove the FODMAPs (Table 2). Particularly vital gluten obtained through their technology is superior to conventionally available vital gluten, which still contains low levels of fructans. However, as explained above, with relatively low addition levels of gluten to product formulations, residual fructans in conventional gluten ingredients are unlikely to contribute to FODMAP levels in the final products, which would exceed a 0.3 g cutoff level for oligosaccharides per food serving. Moreover, several fiber ingredients with an LF claim, which are also isolates from high FODMAP raw material, were available. This included resistant starches and dextrins from pea and wheat, but also partially hydrolyzed guar gum (PHGG) and acacia gum are isolates from GOS accumulating legume seeds (Figure 4) (Singh et al., 1990). These fiber ingredients are LF certified based on the low content of the routinely tested FODMAPs. Furthermore, they are not or only slowly fermentable fibers and could therefore classify as IBS-suitable fiber; however, data on their tolerability in

TABLE 2 Overview of fermentable oligosaccharides, disaccharides, monosaccharides, and polyol (FODMAP) related patents

Invention/claim	Approach to achieve low FODMAP content	Associated commercial product(s)	Assignee/applicant	Inventor
Easily digestible chocolate product (WO 2016/097189 A1; published: 23/06/2016)				
Composition for manufacturing low sugar/sugar-free chocolate products (bars, spreads, fillings, powders, beverages) sweetened with non-FODMAP sweeteners and replacement of whole milk to reduce lactose contents in milk chocolate products.	Replacement of sucrose, sugar alcohols, FOS, inulin, with mogroside-enriched monk fruit extract, isomaltulose and sweet tasting protein (taumatin, monellin, pentadin, brazzein, curculin, miraculin). Replacement of whole milk with milk protein extract or isolate, casein/whey mixtures, soy protein. Potential addition of insoluble and/or slowly fermentable fibers (cellulose, lignin), nuts.	–	Cavalier	Vergedem, F.
Wheat-based products in foods for the wheat intolerant (WO2015117182A1; published: 13/08/2015)				
Production of reconstituted low FODMAP wheat gluten protein-based flour, including other LF isolates from wheat or nonwheat origin and products made from such ingredients result in LF products.	Wheat gluten and other constituent of the reconstituted flour are extracted from wheat and other source material. FODMAPs are removed by washing insoluble material with water or separated from soluble higher molecular weight constituent by membrane filtration.	LO-FO pantry Plain flour	Shoalhaven Starches PTY Ltd	Pearce, R. J.; Barrie, A. L.
Low-fructan grain material and a method for producing the same (WO2016113465A1; published: 21/07/2016)				
Technology allowing efficient removal of fructans from grain material, to be used for LF products.	Seed or purified microbial starter produced with grain material with low damaged starch content (e.g., cut rye kernels) to promote spontaneous formation of microflora of lactobacilli able to efficiently utilize fructans (*L. ultunensis, L. crispatus, L. amylovorus, L. amylovorans, L. sobrius* and/or *L. acidophilus*). Use of the starter for fermentation of high fructan grains (rye, barley, wheat) and various LF products.	Fazer Stomach Friendly Rye Bread (product discontinued)	Oy Karl Fazer Ab	Loponen, J.

(Continues)

TABLE 2 (Continued)

Invention/claim	Approach to achieve low FODMAP content	Associated commercial product(s)	Assignee/applicant	Inventor
Methods of providing FODMAP friendly food items (US2020/0229481 A1; published: 23/07/2020)				
Substitution of onion and garlic in product formulations/recipes to obtain "FODMAP diet friendly" food while maintaining the flavor.	Onion and garlic in conventional recipes are replaced with garlic scapes, spring garlic tops, green tops of leeks, green spring onion tops, chives, green tops of scallions.	Gourmend Foods garlic scape and garlic chive powders, chicken broth	Ketan Vakil	Ketan Vakil
An enzyme exhibiting fructan hydrolase activity (WO2017220864A1; US 2019/0174773 A1; published: 28/12/2017; 13/06/2019)				
Enzyme allowing significant reduction of fructan content in grain and vegetable material/products containing those.	Extracellular fructanase FruA from *L. crispatus* DSM 29598, isolated from rye sourdough (with low damaged starch), recombinantly produces in host cells; enzyme efficiently degrades fructans. Use of enzyme, for example, in combination with baker's yeast to produce LF products.	Fazer Stomach friendly Soft Wheat-Oat Flax Bread, LOFO™	Oy Karl Fazer Ab	Loponen, J.; Mikola, M.; Sibakov, J.
Wholemeal bread with reduced FODMAP content (WO2019034630A1; published: 21/02/2019)				
Production of wheat wholemeal bread with a significantly lowered FODMAP content.	Use of inulinase secreting yeast, *K. marxianus* strains, which efficiently degrade fructans in a co-culture with *S. cerevisiae* to achieve sufficient CO_2 production.	–	Katholieke Universiteit Leuven	Courtin, C.; Struyf, N.; Thevelein, J.; Verstrepen, K.

Abbreviation: LF, low FODMAP.

IBS clinical studies are incomplete (Atzler et al., 2021a; So et al., 2020). The fermentability of PHGG, acacia gum, and different resistant starches (derived from maize and tapioca) was recently tested in an in vitro screening compared to rapidly fermentable short chain fructans, which are known to cause symptoms. With a moderate to very slow fermentability, these fibers were identified as potentially safe fibers to be tested in vivo in IBS patients (So et al., 2020).

Ultimately, the principle of the wheat flour replacement with gluten and starch isolates, fortified with "IBS-safe" fibers could be a cornerstone for the development of beneficial LF bakery products and pasta; it could provide a simple, efficient, and reliable approach for LF products, without the need of any further FODMAP reduction techniques. This is particularly interesting for premanufactured baking mixes which do not require any controlled conditions to reduce FODMAPs at home (i.e., enzymatic, yeast, or sourdough FODMAP reduction during strictly controlled incubation or fermentation conditions). However, further in vitro and in vivo studies are needed to validate the tolerability of different dietary fibers by IBS patients and studies to investigate the fibers' techno-functional and nutritional properties when incorporated in targeted low FODMAP product applications.

3.3 | Impact of cooking during food preparation

Oligosaccharides, including fructans and GOS, but also di- and monosaccharides (glucose, fructose, sucrose, maltose) are well soluble in water and have been shown to diffuse into hot water during the cooking process of pasta and pulses (El-Adawy, 2002; Gélinas et al., 2016; Ispiryan et al., 2020; Stone et al., 2020).

A reduction of GOS (mostly referred to as raffinose family oligosaccharides, raffinose family oligosaccharides (RFO), or α-galactosides in relevant literature) after soaking and subsequent cooking has been reported in a number of studies in a wide variety of pulses, for example, chickpeas, lentils, yellow and green peas, soybeans, or kidney beans. However, the effectivity of the reduction was highly variable (~10%−80%) (El-Adawy, 2002; Han & Baik, 2006; Stone et al., 2020; Tuck et al., 2018). This approach is particularly interesting for the direct consumption of the cooked pulses in meals, where they serve as a rich source of plant protein, dietary fiber, and micronutrients. Nevertheless, because the cooked pulses often contain GOS levels exceeding the cutoff level of 0.3 g per serving (Tuck et al., 2018), satiating servings of pulses still have to be avoided by GOS-sensitive IBS patients (according to serving size recommendations of Monash University mobile phone application). Further targeted studies could focus on identifying optimal soaking and cooking conditions for different types of pulses to achieve a potential reduction resulting in <0.3 g of GOS per serving, which could be either indicated on the product packaging for consumers or used for the production of canned products.

Furthermore, ~40% of durum wheat fructans in pasta are lost in the cooking water (Gélinas et al., 2016; Ispiryan et al., 2020). Nonetheless, a 140 g (Edwards, 2017) serving of the resulting cooked pasta usually contains >0.3 g of fructans (Biesiekierski et al., 2011; Gélinas et al., 2016; Ispiryan et al., 2020). Hence, >90% of the currently commercially available LF pasta products are wheat- and gluten-free products (Figures 3 and 4). However, functional LF pasta could also be produced by partial replacement of the durum wheat semolina with low FODMAP ingredients. For example, for a semolina containing ~1.2% fructans (Ispiryan et al., 2020), the replacement of 20% with alternative ingredients would be sufficient to obtain a cooked pasta with <0.3 g fructans per serving. The substitution of semolina with other nutritionally beneficial ingredients, including fibers or protein-rich ingredients, is an approach that has been of great research interest, primarily aiming an increase in nutritional value compared to conventional pasta (Bustos et al., 2015; Mercier et al., 2016). However, to the best of our knowledge, the FODMAP content has not been considered in any of the researched approaches. Even though the incorporation of some ingredients revealed to be challenging in terms of sensory and technological quality characteristics, advances in pasta research have demonstrated different possibilities. For instance, Hoehnel et al. (2020) have recently shown the benefits of wheat pasta fortification (semolina replaced at a level of ~24%) with a mixture of protein-rich ingredients from buckwheat, fababean, and lupin and achieved an improved high-quality protein profile. As the substitution of semolina with other low FODMAP ingredients (e.g., LF grains, LF protein isolates from pulses, dietary fibers) has not been investigated to date for the production of LF pasta, studies are required on the incorporation of different ingredients and the concomitant consequences. This will aid to identify optimal wheat-based low FODMAP pasta formulations, which do not require further FODMAP reduction techniques.

3.4 | Biotechnological FODMAP reduction

Besides technologies based on the physical removal or avoidance of FODMAPs, functional products can also be obtained with biotechnological FODMAP reduction techniques. Thereby, the main FODMAPs of cereals and pulses, fructans, and GOS can be degraded by added enzymes,

microbial enzymes during a fermentation process, or activated endogenous seed enzymes during a germination process. Biotechnological FODMAP reduction techniques allow for targeted FODMAP degradation and provide products with a good source of wholegrain-intrinsic, beneficial dietary fibers (Laatikainen et al., 2016).

While some fructan accumulating plants such as chicory and cocksfoot (*Dactylis glomerata*) contain linear fructan molecules composed of ß (2 → 1), inulin-type, or ß (2 → 6), levan-type, linked fructose chains with a terminal glucose moiety, it is a characteristic for cereals to contain fructans composed of branched molecules with both types of linkages and a terminal glucose residue (graminan-type) or linear molecules with an internal glucose residue (neo-series-type) (Livingston et al., 2009; Verspreet et al., 2015, 2017). Cereal fructans can be degraded with ß-fructofuranosidases, including invertases (EC 3.2.1.26), fructan exohydrolase (EC 3.2.1.80), and endohydrolase (EC 3.2.1.7; fructan hydrolases are commonly referred to as inulinases or fructanases; the term inulinases will be used in this review). Both invertases and exo-inulinases catalyze the hydrolysis of terminal nonreducing moieties, while fructan chains are hydrolyzed to fructose monomers and the glucose unit. Endo-inulinases cleave internal glycosidic bonds and thereby produce several shorter fructan chains. Although invertases have a higher specificity toward shorter fructan chains (average degree of polymerization [DP] ~5), inulinases also quickly degrade long-chain fructans (Nilsson et al., 1987; Struyf, Laurent, Verspreet, et al., 2017). With average DPs of 5–7 in wheat (Ispiryan et al., 2019; Verspreet et al., 2015), both enzymes are capable of hydrolyzing the majority of wheat fructans under optimal conditions (Struyf, Laurent, Verspreet, et al., 2017).

The indigestible α-galactosyl linkages in GOS (raffinose, stachyose, verbascose) are cleaved by α-galactosidases (EC 3.2.1.22), which results in the release of 1–3 galactose units and sucrose. Even though ß-fructofuranosidases also technically reduce the amount of raffinose, stachyose, and verbascose through the action of the enzyme on the sucrose-end of the saccharides, their indigestible linkages remain intact (Atzler et al., 2020). The resulting degradation products, besides the released fructose (namely melibiose, manninotriose and manninotetraose) are still accounted as FODMAPs.

An important key element of this approach is that the oligosaccharide degradation should always be linked to a strategy for reducing the resulting degradation products in order to avoid an accumulation of other FODMAP carbohydrates. In addition, notwithstanding that some of the principles of these methods have been applied for food production for centuries (i.e., yeast leavening and sourdough fermentation for breadmaking), it is important to approach them now as targeted FODMAP reduction strategies. Strictly controlled and defined process parameters and product formulations are essential to achieve the required FODMAP reduction.

3.4.1 | Addition of purified enzymes

The purified enzyme preparations can be of plant or microbial origin (Nyyssölä et al., 2020). Food grade ingredients of the enzymes, specifically produced for food and beverage applications are available, for instance, from Creative Enzymes: endoinulinase and exoinulinase from *Aspergillus niger* (NATE 1245 and 1246), invertases from baker's yeast (NATE-0357) or *Candida* sp. (DIA-205), and α-galactosidase from *A. niger* (DIS-1012).

The most relevant enzymes for bakery products and pasta are invertases and inulinases. These will degrade cereal fructans to fructose and glucose (Atzler et al., 2020; Struyf, Laurent, Verspreet, et al., 2017). Even though GOS (i.e., raffinose) levels are also expected to be quickly reduced, the resulting melibiose and fructose still contribute to the total FODMAP content, such as the fructose from sucrose, raffinose, and fructans (Atzler et al., 2020). Hence, linked purely enzyme- or fermentation-based solutions are required. For bakery products, combining baker's yeast fermentation in a simple yeast-leavened bread or using sourdough technology are the most favorable approaches (CO_2 production in glycolysis by microorganisms essential for the leavening). Yeast and specific LAB utilize the fructose, released from the enzymatic degradation of the saccharides, during the fermentation and proofing of the products. The synergistic effect of added enzymes, yeast, and LAB is an effective strategy to lower total FODMAP contents. Acín Albiac et al. (2020) have recently demonstrated the potential of the combination of a commercial invertase preparation (added at a level of 1 U/10 mg fructan) in a wheat sourdough with potent strains of fructophilic lactic acid bacteria (FLAB). These microorganisms were capable of utilizing the fructose released from the fructan degradation without distinct accumulation of mannitol, a common LAB metabolite in sourdough. Moreover, Li et al. (2020) applied a commercial exo-inulinase containing baking ingredient (Fazer LOFO, 1% based on flour, activity not reported) in a wheat–rye sourdough and straight dough yeast-leavened bread and achieved complete fructan degradation and very low fructose and mannitol levels. Alternatively, enzymes such as amyloglucosidase and amylases to release glucose from starch and decrease the amount of fructose present in excess to glucose could be used (Melim Miguel et al., 2013). However, increased levels of free glucose and fructose in products may have several disadvantages

concerning sensory (too sweet) and nutritional (increased glycemic index) attributes. Pasta is possibly the only product, where additional techniques for excess fructose removal may not be required, as it is expected that the free fructose will largely leach into the cooking water (Gélinas et al., 2016). If a sufficient fructan and fructose reduction is achieved via enzyme-based fructan degradation and fructose-consumption by baker's yeast or LAB, low levels of melibiose resulting from the raffinose degradation have a comparably minor impact on the total FODMAP content (if wheat is the only GOS containing ingredient). Nevertheless, it is still essential to consider melibiose levels when calculating the total FODMAP content, for example, melibiose from a complete degradation of ~0.2% raffinose from the flour would already account for ~15% of the maximal tolerated oligosaccharide level of 0.3 g/50 g of bread. An additional strategy for the degradation of the α-galactosyl linkages in GOS may be necessary if the fortification of cereal-based products with pulses is considered. Fortification of wheat-based products with pulse flours is emerging, as it offers, among other advantages, an excellent possibility to increase the nutritional quality of the plant protein composition (Boukid et al., 2019). Such products do not have to be avoided in low FODMAP applications, as a combination of inulinases/invertases and α-galactosidases can be applied to degrade fructans as well as GOS. A recent study demonstrated the potential of α-galactosidase application in different pulse-based product prototypes (meat analogues, crackers, spoonable products) to lower GOS levels by up to >90% (Nyyssölä et al., 2021). Furthermore, the use of α-galactosidases has been described in soy-based milk alternatives to lower GOS contents (Nyyssölä et al., 2020).

Among the commercially available LF products, there was one bread where the above-mentioned exo-inulinase containing ingredient LOFO was used in combination with baker's yeast fermentation to produce a wheat-based LF bread. According to the manufacturer's claim, the bread has 0.2 g/100 g FODMAPs. The production of the LOFO ingredient is based on a patented technology by Loponen et al. (2017) (Fazer Mills, Finland; Table 2). It contains an exo-inulinase (FruA), isolated from *Lactobacillus crispatus* DSM 29598 and recombinantly produced in host cells such as *Pichia pastoris*. The inulinase expressing *L. crispatus* was in turn isolated from a sourdough and has been shown to efficiently degrade fructans in a sourdough system (Li et al., 2020; Loponen, 2016; Loponen et al., 2017). In an application example of the patent, the inventors describe a dosage of 0.18% enzyme based on flour (e.g., 1 U/18 mg fructan for 500 U/g activity of enzyme preparation stated in patent) in a wheat bread that was made in a straight dough process with 3% baker's yeast and 1.8% sucrose. The enzyme was added to the formulation suspended in the water of the recipe, and the dough was left to rise for 2 h at 37°C. The resulting bread had a fructan concentration of 0.05%, which was reduced by ~90% compared to the flour. However, the fructose concentration in the bread was 0.4% which may exceed the cutoff value of 0.15 g/50 g of bread for excess fructose if glucose concentrations in the bread were lower than 0.1% (levels not reported). In such cases, a higher dosage of the enzyme may allow for a faster fructan degradation and hence more efficient fructose consumption by the yeast over the fermentation period. Atzler et al. (2020) reported an almost complete inulinase-mediated degradation of wheat fructans in an aqueous solution already after 1 h with 1 U enzyme per 0.001 mg fructans. To fully validate the application of purified enzymes in low FODMAP baking, further studies are required to identify optimal process parameters (i.e., enzyme dosage, fermentation time and temperature, product formulations) using commercially available food grade enzyme preparations.

3.4.2 | Yeast- and LAB-mediated FODMAP reduction

Specific strains of yeast and LAB can express invertases, inulinases, or α-galactosidases which degrade the oligosaccharides during the fermentation of a production process. Yeast and LAB are powerful tools for FODMAP reduction in bakery products, but not a guarantee, unless targeted methods with selected starter cultures and defined process parameters are used, rather than short fermentation industrial bread-making methods or conventional sourdoughs.

Baker's yeast (*Saccharomyces cerevisiae*), the most commonly used leavening agent in industrial baking, can express invertase (Nilsson et al., 1987; Sainz-Polo et al., 2013). It was shown that yeast invertase-mediated release of fermentable carbohydrates (from sucrose, raffinose, and fructans) plays an essential role in the bread-making process, apart from maltose, providing glucose and fructose as substrates for CO_2 production, particularly in the first hour of fermentation (Struyf, Laurent, Lefevere, et al., 2017). Yeast invertase has a higher affinity toward short chain fructans and quickly degrades up to DP ~5 fructans in the first hour of fermentation. In contrast, the degradation of higher DP fructans is slower (Nilsson et al., 1987). Nonetheless, several studies reported that ~40%–90% of the initially present fructans in wheat flour are degraded by yeast invertase during the bread-making process (Gélinas et al., 2016; Knez et al., 2014; Laurent et al., 2020; Longin et al., 2020; Nilsson et al., 1987; Pejcz et al., 2019; Schmidt & Sciurba, 2021; Struyf, Laurent, Verspreet, et al., 2017; Struyf et al., 2018; Ziegler et al., 2016). For example, a white wheat bread made with flour that contains ~1.2%

fructans would require only ~30% fructan degradation to result in a bread with fructan levels below the cutoff of 0.3 g/50 g bread (considering a moisture of 40% in bread). A wholemeal bread with ~2% initial fructans from the flour would require ~60% fructan degradation. However, even though the yeast partly metabolizes the released fructose, insufficient fermentation times can result in excess fructose levels exceeding 0.15 g/50 g bread, despite the fructans being degraded. Ziegler et al. (2016) have first shown the significance of extended fermentation and proofing times for low FODMAP baking with baker's yeast. After 1 h of fermentation and proofing, they had already achieved a fructan degradation of 60%, but fructose released from raffinose, sucrose, and fructans led to a level of ~1% excess fructose in the bread. An extended fermentation time of 2.5 h, in contrast, allowed for a reduction of the excess fructose by ~70% and overall low FODMAP levels (4.5 h of fermentation even resulted in >90% fructan degradation and only 0.03% excess fructose). However, fermentation times of industrial bread making (e.g., Chorleywood process commonly used in the United Kingdom [Delcour & Hoseney, 2010]) may often be too short for achieving sufficiently low FODMAP levels, especially in wholemeal bread (Schmidt & Sciurba, 2021). Besides the fermentation and proofing times, other factors such as the yeast addition level (Struyf, Laurent, Verspreet, et al., 2017), the extraction rate of the flour (i.e., refined flour vs. wholemeal flour) (Schmidt & Sciurba, 2021), and other sources of fermentable sugars in the ingredients (e.g., added sucrose) (Struyf, Laurent, Verspreet, et al., 2017) are decisive for the final FODMAP content. Furthermore, Li et al. (2020) demonstrated the limitation of baker's yeast to achieve sufficiently low FODMAP levels in rye- and wheat- (in equal parts) based bread, as rye contains significantly more fructans than wheat (~4% vs. ~2% in wheat). Despite a 56% fructan degradation and relatively low fructose levels after 3 h of fermentation and proofing, the remaining fructan levels still exceeded 0.3 g/50 g bread. Hence, although conventional baker's yeast has the potential to be applied in low FODMAP baking, a targeted approach considering the described factors is essential. Currently, only 10 of the commercially available breads with an LF claim could be categorized as low FODMAP due to the effect of baker's yeast fermentation (Figure 3). Furthermore, one wheat flour was available, marketed as "2ab wheat" (made from an ancient wheat species *Triticum turgidum* forma *sanum*), claimed to have a lower FODMAP content than common bread wheat flour due to the prefermentation of the flour with yeast (Kautz, 2017).

As an alternative to conventional baker's yeast, different non-*Saccharomyces* yeast species have proven their potential to efficiently lower FODMAP contents in a wholemeal wheat bread (Courtin et al., 2019; Laurent, Struyf, et al., 2021; Struyf, Laurent, Verspreet, et al., 2017; Struyf et al., 2018). Strains belonging to *Kluyveromyces marxianus* species have been shown to degrade fructans much more efficiently due to cell wall–associated inulinases and the expression of those into the fermenting dough, in contrast to *S. cerevisiae* species, which degrade fructans solely with cell wall invertases. As *K. marxianus* species are unable to ferment maltose, they need to be used either in a coculture with *S. cerevisiae* or require an alternative carbohydrate source (e.g., added sucrose or amyloglucosidase to release glucose from starch) to achieve an appropriate dough rise. But even with the additional sources of carbohydrates, resulting breads were shown to have fructan contents by far below the cutoff levels, owing to the yeast's unique ability to express extracellular inulinases (Struyf, Laurent, Verspreet, et al., 2017; Struyf et al., 2018). Furthermore, another non-*Saccharomyces* yeast strain, originating from a Kombucha culture, *Lachancea fermentati* FST 5.1, has also been shown to degrade fructans more efficiently than conventional baker's yeast and resulted in bread with high quality characteristics (volume, texture, aroma), comparable to baker's yeast. The underlying fructan degradation mechanism remains to be elucidated (Ispiryan, Borowska, et al., 2021). Moreover, a *Torulaspora delbrueckii* strain, isolated from a sourdough culture, appeared promising with a higher fructan reduction rate than baker's yeast in a wheat flour slurry (Fraberger et al., 2018). A targeted application of the strain in products, however, has not been reported yet. Also, the potential of different *S. cerevisiae* strains from bakery and other industrial applications with pronounced high invertase activities and fructan substrate specificities for their use in low FODMAP baking applications has been recently demonstrated (Laurent et al., 2020; Laurent, Aerts, et al., 2021).

In sourdough baking, LAB represent an additional group of microorganisms besides yeast. Bread formulations typically contain approximately 20% sourdough. Industrial sourdough bread production often also includes baker's yeast as a leavening agent. The added sourdoughs can be produced either by spontaneous fermentation (forming natural microflora through repeated reinoculation of the dough with water and flour) or by propagating with starter cultures. Different types of sourdough (i.e., types I and II) are characterized by their dough yield (amount of dough obtained from 100 parts of flour), fermentation conditions, and the prevalent microflora (Arendt et al., 2007; Gobbetti & Gänzle, 2013; Loponen & Gänzle, 2018). As Loponen and Gänzle (2018) reviewed, the application of sourdough technology for low FODMAP baking can be compelling but is much more complex than yeast fermentation due to the high diversity of LAB microflora under different conditions and their concomitant metabolic processes. Several factors accentuate the

necessity for targeted sourdough fermentation rather than conventional sourdough techniques, especially for the production of whole wheat or rye-based sourdough bread (Pejcz et al., 2020; Schmidt & Sciurba, 2021). First, fructan degradation by LAB is often limited to intracellular hydrolysis of short chains (DP < 4) with ß-fructosidases (SacA, SucP), as oligosaccharides with higher DP cannot be transported into the intracellular area (Gänzle, 2020; Loponen & Gänzle, 2018). Furthermore, heterofermentative LAB do not utilize fructose as a carbon source but reduce it to mannitol; therefore, fructose serves as an electron acceptor for the regeneration of reduced cofactors. Another undesired attribute of LAB for low FODMAP baking is that certain species can produce exopolysaccharides (EPS) composed of fructose monomers (levan, inulin, fructooligosaccharides). Both mannitol and EPS production in relevant levels, however, are linked to the presence of endogenous or added sucrose in the formulation (Loponen & Gänzle, 2018). Furthermore, LAB can hydrolyze GOS through the action of levansucrase, α-galactosidase, and sucrose phosphorylase activity. However, as not all species express α-galactosidase activity, the fermentation of GOS rich material (i.e., pulses) can lead to the accumulation of melibiose and its higher oligosaccharides. Levansucrases (glycosyltransferases) in turn, which release fructose from the sucrose end of GOS, can also catalyze the synthesis of fructans (Teixeira et al., 2012; Tieking et al., 2003).

Research over the past few years has proposed highly efficient sourdough-based LF baking approaches. Even though extracellular exo-inulinases (mostly referred to as fructanases in relevant literature) are rare in LAB, few species have been identified to express two different exo-inulinases: FruA and FosE. The aforementioned strain *L. crispatus* DSM 29598 (obligate homofermentative) expressed FruA and was isolated from a sourdough described in a patent application. According to the inventor, the growth of fructan-degrading LAB could be promoted by choice of flour with low damaged starch content, as in such case, fructan rather than starch is readily available as a source of fermentable carbohydrates (Loponen, 2016). Wheat- and rye-based bread prepared with 20% *L. crispatus* fermented sourdough (16 h, 37°C; bread dough fermentation 3 h, 37°C) and 2% yeast was shown to contain very low FODMAP levels, far below all individual cutoff levels. The use of heterofermentative *Limosilactobacillus reuteri* or *Limosilactobacillus frumenti*, either in co-culture with *L. crispatus* or with 1% addition of FruA containing LOFO ingredient resulted in higher mannitol concentrations, yet still FODMAP levels below the cutoff levels. This synergistic effect of the highly efficient fructan degrading LAB or the FruA containing ingredient combined with baker's yeast was capable of degrading the majority of the wheat and rye-derived fructans, without the accumulation of fructose or mannitol (Li et al., 2020). Two clinical trials comparing the symptom induction of a conventional rye sourdough bread and a sourdough bread made with the *L. crispatus* strain provided evidence for a better tolerability of the sourdough bread made with the potent strain (exact process parameters and product formulations unknown, but only *L. crispatus* fermented bread had FODMAP contents below the cutoff levels) (Laatikainen et al., 2016; Pirkola et al., 2018). Phylogenetic analysis of exo-inulinases in LAB showed the presence of FruA in the genomes of *Ligalilactobacillus salivarius*, *Ligalilactobacillus equi*, *Latilactbacillus curvatus*, *Lb. amylovrus*, and *Lb. delbrueckii*. The second exo-inulinase FosE was characterized in *Lacticaseibacillus paracasei* and homologues were found in the genomes of *Lacticaseibacillus casei*, *Lactiplantibacillus plantarum*, *Pediococcus pentosaceus*, *Pediococcus acidilactici*, and *Liquorilactobacillus* spp. (taxonomy according to recent reclassification of genus lactobacillus (Zheng et al., 2020)) (Li et al., 2020). Another concept that has been recently described for low FODMAP sourdough baking is the use of strictly FLAB. In contrast to other LAB, these prefer fructose over glucose as growth substrate and utilize it as a carbon source and an electron acceptor while producing mannitol, which in turn can be used too. The authors identified a potent combination of two FLAB strains with maximal fructose (*Aplilactobacillus kunkeei* B23I) and mannitol consumption rates (*Fructobacillus fructosus* MBIII5), which were applied in a preliminary baking experiment in combination with commercial invertase. The resulting bread made from refined wheat flour had very low total FODMAP contents of ~0.3% dm (based on dry matter, corresponds to ~0.08 g/50 g of fresh bread), which is far below the cutoff levels. An application of this concept in a more challenging bread system (e.g., based on whole rye and wheat) has not been described yet, but seems promising. The production of a low FODMAP bread from refined wheat flour using conventional bread-making techniques (with or without sourdough) seems rather not challenging. Different studies reported low fructan, mannitol, and fructose levels in refined wheat-based sourdough breads prepared with varying combinations of homo- and heterofermentative LAB (Fang et al., 2021; Menezes et al., 2019, 2021; Schmidt & Sciurba, 2021). In contrast, the synergistic effect of *L. plantarum* and baker's yeast was shown to efficiently lower fructan contents in whole wheat sourdough breads (<0.3% dm). When rye flour was used, however, remaining fructan levels were >2% dm (other FODMAPs were not reported but may have been high in both sourdough breads). Also, different whole wheat- or rye-based sourdough breads made with baker's yeast and commercial sourdough cultures (with the yeast *Candida milleri* and heterofermentative *Fructilactobacillus*

sanfranciscensis) were reported to contain fructan and/or excess fructose and mannitol levels exceeding the cutoff levels (Schmidt & Sciurba, 2021). Another recent study reported particularly high mannitol levels >2% in sourdoughs prepared with a commercial starter culture (Pitsch et al., 2021).

Further studies should focus on applying the above-described targeted concepts, investigate the synergistic effects of purified enzymes and potent yeast and LAB strains, and explore possibilities for their application in different formulations of bakery products, especially those containing high portions of whole rye flour or fortified products with pulses. Currently available commercial products with an LF claim, which were categorized as LF due to the use of sourdough technology, included 12 breads, two pizza bases, and two pasta products, while only three of the products contained a small portion of rye flour (Figures 3 and 4).

3.4.3 | Activation of endogenous seed-enzymes

Endogenous seed enzymes can act to hydrolyze storage carbohydrates and are activated or synthesized during the germination process of seeds. Low temperatures and high moisture (condition achieved by soaking of grains, called imbibition) initiate the germination process and stimulate the production of plant hormones, which in turn stimulate the production of endogenous enzymes (Bewley et al., 2013). These modify the seeds' composition and nutritional value, which is important for malted or sprouted ingredients, used for brewing purposes or as functional ingredients in bakery products and fresh sprouts for direct consumption. The germination process positively contributes to the flavor and increases bioactive compounds and minerals in cereals, pseudo cereals, and pulses (Kaukovirta-Norja et al., 2004; Mäkinen & Arendt, 2015). Although with the correct use of terminology, the germination is terminated with the protrusion of the seedcoat by the radicle (Bewley et al., 2013), most literature includes observations made during the following stage of the seedling growth when referring to the germination process. Hence, the impact of germination on FODMAP carbohydrates discussed in the following includes both the actual germination and the following seedling growth stage.

During the germination process, α-galactosidase activities, which act to hydrolyze the indigestible linkages in raffinose, stachyose and verbascose, are increased (Blöchl et al., 2008; Lien et al., 2018; Reddy & Salunkhe, 1980). The potential of germination to decrease GOS levels in a wide variety of pulses has been extensively studied and proven to be effective in up to the complete removal of these saccharides, as reviewed by Nyyssölä et al. (2020). While germination under light and dark conditions does not seem to affect the GOS degradation (Vidal-Valverde et al., 2002), the extent of the degradation directly correlates with the germination time, as the content of oligosaccharides constantly decreases (Wang et al., 1997). Germination has also been shown to be effective in the reduction of GOS in cereals and pseudo cereals, as well as other α-galactosides, such a fagopyritols in buckwheat (Gamel et al., 2006; Harris & MacWilliam, 1954; Horbowicz et al., 1998; Jia et al., 2015; MacWilliam et al., 1956). Despite a large number of studies reporting a significant reduction of GOS upon 2–6 days of germination, Tuck et al. (2018) observed elevated GOS levels in sprouted chickpeas. Germinating seeds contain anabolic as well as catabolic enzymes, and the GOS catabolism typically predominates. But if the germination process is impaired, for example, due to desiccation, GOS biosynthesis may be initiated (Blöchl et al., 2008). This highlights the importance of controlled germination conditions to achieve the desired degradation. Ultimately, sprouted or malted pulse ingredients may serve as valuable ingredients in low FODMAP formulations to increase the nutritional value of cereal-based products, but also for the direct consumption as fresh sprouts on salads or cooked pulses in meals. The enzymatic degradation during germination combined with physical removal of GOS during cooking is particularly powerful for GOS reduction. However, the latter applications require further studies to clearly define the germination conditions needed to achieve sufficiently low GOS levels in different kinds of pulses, which could then be indicated on the product packaging for the consumers.

In contrast to the well-studied metabolism of GOS during the germination of different seeds, biochemical changes concerning the fructan metabolism during the germination of cereals have received much less attention. Still, a few studies reported a clear trend of fructan development during the malting process (Cozzolino et al., 2016; Harris & MacWilliam, 1954; Ispiryan, Kuktaite, et al., 2021; Krahl et al., 2008; MacWilliam et al., 1956), supposedly also controlled by different anabolic and catabolic enzymes of the fructan metabolism in plants (invertases, fructan hydrolases, fructosyltransferases), as discussed in our recent study (Ispiryan, Kuktaite, et al., 2021). An initial, slight decrease during the imbibition (steeping) is followed by a significant increase in fructans upon 3–9 days of germination, followed by partial decomposition during the kilning (final drying step of the process). Green malts (sprouted grains before kilning) from barley, wheat, and spelt were shown to contain 30%–300% higher fructan levels than the raw grains, depending on the duration of the germination time (Harris & MacWilliam, 1954; Krahl et al., 2008; MacWilliam et al., 1956). Germinated oat

contained even 1.4% dm de novo synthesized fructan, while the raw grains contained only traces (Ispiryan, Kuktaite, et al., 2021). Despite the decrease during the kilning step (up to ~50%), the fructan content of the malts from barley, spelt, and wheat was reported to be still 10%–60% higher compared to the raw material, and oat malt still contained 0.8% dm fructans (Cozzolino et al., 2016; Ispiryan, Kuktaite, et al., 2021; Krahl et al., 2008; MacWilliam et al., 1956). Although Krahl et al. (2009) reported no significant changes in the fructan content in malted barley, this may be explained by the impact of kilning which may have compensated for an increase during the germination. In clear contrast to this stand the findings of Tuck et al. (2018), they reported lowered fructan levels in sprouted wheat, barley, and rye grains. However, as the results are reported based on the fresh weight and sprouts contain approximately 50% water, compared to dry seeds which contain 10%–15% water, this effect might be, at least partly, explained by dilution of the fructans. Nonetheless, further studies should investigate whether variations in the germination process (e.g., imbibition time and conditions, exposure to light) can shift the metabolism of fructans toward a prevalence of the catabolism. Indeed, two commercially available breads with an LF claim were solely made from sprouted grains from spelt and kamut (Figure 3). Both types of grains have been shown to contain comparable fructan levels to bread wheat (Gélinas et al., 2016; Longin et al., 2020; Ziegler et al., 2016). Hence, a degradation of the fructans during the sprouting process is likely and deserves more scientific attention.

4 | FOOD SCIENCE AND REGULATORY MECHANISMS FACING LIMITATIONS WITH THE CURRENT VIEW OF FODMAPS UND FUTURE PERSPECTIVES

Over the past few years, substantial research efforts have already revealed promising and powerful tools for the production of low FODMAP functional products. Those are based either on avoiding high portions of FODMAP-rich ingredients in product formulations or on biotechnological FODMAP reduction strategies mediated by added enzymes, microbial enzymes during a fermentation process and endogenous enzymes during a germination process. The strengths, limitations, and possible solutions for available approaches are summarized in Figure 6. Further studies should focus on combined approaches (i.e., replacement of parts of high FODMAP ingredients, added enzymes, potent yeast, and LAB species) and investigate the different synergistic effects in a larger variety of products and product formulations (i.e., including different whole grains and pulses in bakery products, pasta, extruded products). Moreover, an industrial-scale production of low FODMAP processing ingredients, including affordable commercial food grade enzyme preparations with required functionalities, as well as potent yeast and LAB starter cultures, is necessary. Ultimately, alongside the effort to identify effective and reliable FODMAP reduction strategies, it should be emphasized that complete removal of FODMAPs is not desirable. Particularly fructans are important prebiotics and should only be reduced as much as required (Muir et al., 2019). Varney et al. (2017) reported cutoff levels that were set conservatively, and their reliability was tested in a number of studies (Barrett et al., 2010; Halmos et al., 2014; Ong et al., 2010).

Furthermore, it seems inevitable to address several factors that complicated the interpretability of current scientific literature. Studies investigating FODMAP reduction strategies often solely report results on the "main FODMAP." An in-depth understanding of the (FODMAPs) degradation mechanisms, the degradation products formed, and their consequences is the golden rule of any targeted biochemical modifications during food processing. Moreover, studies refer to various cutoff levels resulting from older studies where the currently known levels were not standardized and published yet. However, if the FODMAP concept is to be accepted based on scientific evidence and implemented in regulatory mechanisms and food production, the adaptation of the most recent and valid cutoff levels (Muir et al., 2019; Varney et al., 2017) must be acknowledged and applied consistently to analytical results based on the fresh weight of products as they would be consumed (not the dry weight). Importantly, accurate and suitable analytical approaches are necessary with clearly defined target analytes, minimal required detection limits, and concomitant interferences and errors. Especially the sufficiently accurate analysis of fructans is challenging. To name a few factors: (1) Studies where fructan analysis was conducted using photometric enzyme assays tend to report very low values; it should be noted that those methods have relatively high detection limits (0.2%–1% depending on the assay used). This means that any values reported below those limits are somewhat not meaningful. (2) Several studies used the Megazyme Fructan HK assay kit (K-FRUCHK) to quantify fructans in cereals, pulses and products made from those. However, because high sucrose, fructose, glucose, and maltose levels in sample extracts (such as it is the case for cereal-based products) result in high blank values, the accuracy of low fructan levels is strongly impaired. Hence, the Fructan assay kit (K-FRUC), which eliminates absorbance from nonfructan-derived reducing sugars with the inclusion of a borohydride reduction step, is better suitable for such samples. (3) Regardless of which photometric enzyme assay kit or other enzymatic

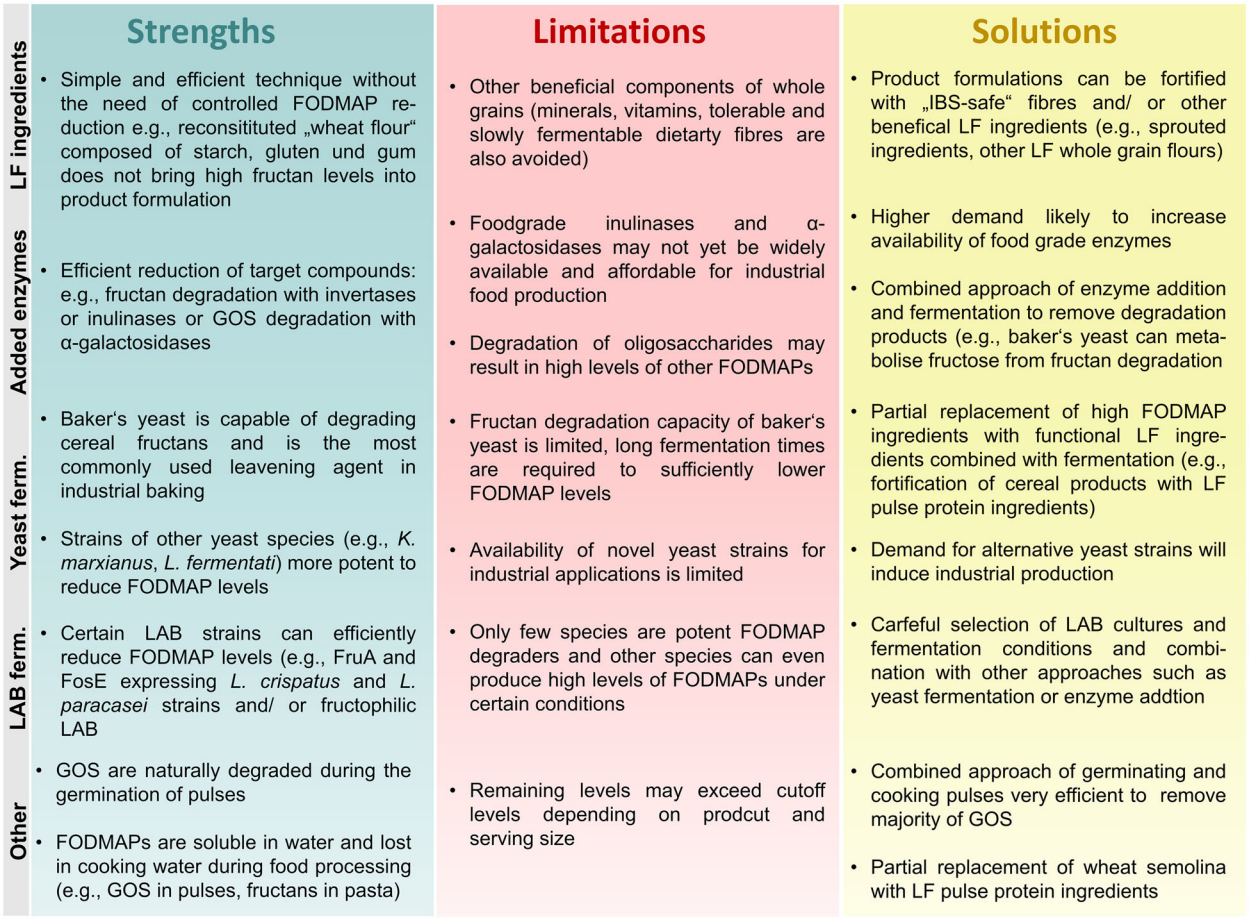

FIGURE 6 Summary of strengths, limitations, and possible solutions for currently available FODMAP reduction techniques

approaches are used, it is important to consider that the fructan degrading enzyme preparation (exo-inulinase and endo-inulinase) also releases fructose from raffinose, stachyose and verbascose (Ispiryan et al., 2019); hence, as advised in the manufacturer's protocols for the assay kits, an additional α-galactosidase treatment of material that contains these sugars is essential to not overestimate the fructan content.

Finally, in close cooperation of biomedical and food scientists, further research is necessary to elaborate on carbohydrates, comprised under the acronym FODMAPs. As highlighted in two recent reviews, the typically listed group of FODMAP carbohydrates includes the vast majority of such but is not limited to them (Gibson et al., 2020; Halmos & Gibson, 2019). So et al. (2021) recently investigated the in vitro fermentability and hence "FODMAP-potential" of xylo-oligosaccharides (XOS) derived from maize and almond shell and reported a high fermentability of the maize-derived XOS (similar to fructans) and a low fermentability of the almond shell-derived XOS. Furthermore, they also identified a rapid fermentability of a carrot peel-derived mixture of cellulose, hemicellulose, and pectin (So et al., 2020). Further in vitro and in vivo studies are needed to identify other carbohydrates with FODMAP potential. Relevant carbohydrates should be included into the routinely analyzed list of FODMAPs, to enable the broadening of the knowledge on their natural occurrence and potentially incorporate them into food testing programs. Also, the relevance of other passively absorbed monosaccharides and brush-border hydrolase deficiencies within the FODMAP concept, and a potential inclusion of affected highly abundant carbohydrates (such as sucrose) should be elucidated. The identification of other potential triggers may lead to an even higher success rate of the low FODMAP diet.

5 | CONCLUSION

Although the low FODMAP diet has great potential for improving the quality of life of individuals suffering from IBS, the food choice for nutritious functional food products to replace the high FODMAP foods is strongly limited. Especially the substitution of healthy, yet high FODMAP, whole-grain and pulse-based products is challenging. The global market of functional foods with a low FODMAP

claim is currently dominated by gluten-free products which also coincide to be low in FODMAPs. However, gluten is an essential component of bakery products and pasta and does not have to be eliminated. In addition, gluten-free products are often characterized by inferior nutritional and sensory characteristics. Given that the concept of the low FODMAP diet has been first described only ~15 years ago, research on the development of functional low FODMAP foods is still in its infancy. Nevertheless, powerful techniques have been presented in recent years, based on the physical removal or biotechnological degradation of FODMAPs, while maintaining product quality. While further research should focus on the investigation of synergistic effects of different approaches in a larger variety of products and products formulations, it is crucial to comply with the scientific consensus (i.e., accurate and standardized analytical methods with clearly defined analytes, most recent cutoff levels as benchmarks). Finally, only the establishment of a regulatory framework implementing the low FODMAP criteria will allow for food manufacturers and consequently consumers to benefit from the scientifically proven technologies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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16 CFR § 255.3 Code of Federal Regulations. Expert endorsements.

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