

Gluten-free products in celiac disease: Nutritional and technological challenges and solutions

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In celiac patient exposure to even only a small amount of gluten can lead to malabsorption of some important nutrients including calcium, iron, folic acid, and fat-soluble vitamins because of small-intestine inflammation. A strictly followed gluten-free (GF) diet throughout the patient's lifetime is the only effective treatment for celiac disease; however, elimination of gluten from cereal-based product leads to many technological and nutritional problems. This report discusses different substitutes to replace gluten functionality and examines the economic and social impacts of adherence to a GF diet. Better knowledge about the molecular basis of this disorder has encouraged the search for new methods of patient treatment. The new and common GF sources and different challenges encountered in production and consumption of these products and different solutions for improving their properties are discussed in this review.

Key words: Celiac disease, enzyme, gluten free, nutrigenomics, substitutes

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INTRODUCTION

Celiac disease is a chronic inflammatory disorder of the intestine which being asymptomatic to causing severe malnutrition.^[1] The prevalence of celiac disease is <0.5%–1% worldwide.^[2] Gluten is the storage protein of wheat and includes glutenin and alcohol-soluble gliadin. Gliadin and other prolamins in rye (secalins) and barley (hordeins) are toxic for patients with celiac disease.^[3] A gluten-free diet (GFD) is the mainstay of celiac disease treatment.^[3] Adherence to a GFD improves many clinical and serological symptoms^[4] and reduces the incidence of malignancies.^[5] Furthermore, it can prevent the development of many autoimmune diseases such as hematologic disorders, hepatitis, and

inflammatory bowel and insulin-dependent diabetes mellitus diseases.^[6] While a limited amount of gluten is permitted in a celiac patient's diet, the amount of tolerable gluten varies widely between 10 mg and 34–36 mg gluten per day.^[7] This has led to confusion about labeling "GF" products. For example, in Canada, such products must meet standards of <20 ppm gluten (20 mg gluten/1 kg), whereas other countries specify a maximum of 200 ppm.^[8] However, producing food that provides a daily gluten intake of <10 mg is acceptable.^[7] Omitting or reducing gluten lowers the quality of end products; this could be overcome with gluten substitutes. This paper aims to review the current knowledge on different GF cereals and gluten substitutes used for the production of GF food and the recent advances in molecular knowledge of celiac

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disease which can help in the development of new methods for celiac therapy.

DIFFERENT SOURCE OF GLUTEN-FREE FLOUR

Hitherto, total lifelong avoidance of gluten ingestion has remained the primary treatment for celiac disease. The overall objective of the GFD is maintaining health through the adoption of a well-balanced diet without using gluten. Observing a strict GFD is not easy, not least because it contributes to the social isolation of patients with celiac disease. In addition, nutritional deficiencies in Vitamins D and B, iron, zinc, calcium, magnesium, and fiber may occur. Furthermore, developing good-quality GF products could be challenging due to the unique properties of gluten.^[9]

Rice

Several significant properties of rice – it lacks gluten, has a bland taste, is colorless and hypoallergenic, has low levels of protein, sodium, fat, and fiber, and contains high amounts of easily digested carbohydrates – make it suitable for making flour that can be used to prepare GF products. As rice contains a relatively small amount of prolamin, it is necessary to combine it with some sort of gum, emulsifier, enzymes, modified starch, or dairy products to obtain viscoelastic properties.^[10] The color of the crust and texture characteristics of acidic extruded rice-flour bread is been found to be similar to those of wheat bread, but it has a low specific volume.^[11] Rice–noodle products are important foods in many Asian countries. Since rice protein cannot participate in the forming of a cohesive dough structure, gelatinized starch plays a role as a binder.^[12] Rice can also be formed into flakes: rice is cooked, coated with skim milk as a nutritious ingredient, and then partially dried, tempered, passed through flaking rolls, and toasted in an oven. Crackers can be also obtained using either nonwaxy or waxy rice.^[13] Technological characteristics of rice-flour products could be improved by the addition of a protein source such as spirulina.^[1,14]

Oats

The high protein, fat, and fiber content of pure oats make them a suitable choice for celiac patients.^[15] However, the safety of oats in a GFD has been questioned in some studies due to possible contamination of the oats with gluten-containing cereals^[16,17] during growing cycle in the farm, cleaning, transportation, storage, or processing. Therefore, it is necessary to extend strategies that would supply uncontaminated oats. The Professional Advisory Board of the Canadian Celiac Association in cooperation with Health Canada had reviewed the literatures on pure oat safety in celiac disease and had recommended the consumption of only limited amount of pure oats about 20–25 g/day (65 ml or ¼-cup dry-rolled oats) for celiac children and 50–70 g/day (125–175 ml or ½ to ¾-cup dry-rolled oats) for celiac

adults.^[18] Fermented oat slurry provides a yoghurt-type product that can be used by patients with celiac disease, lactose intolerance, or a milk allergy.^[19] Moreover, oat β-glucans are technologically feasible thickening agents in soups and have high acceptance among consumers.^[13]

Pseudocereals

In contrast to the most common grains, pseudocereals are composed mainly of albumins and globulins and contain very little or no storage prolamin proteins;^[18] thus, they are good substitutes for cereal in GF foods. The nutritional values of wheat and different important GF flour are compared in Table 1.^[18]

Amaranth

Amaranth consists of small seeds with a nutritional value better than that of any other vegetable, including cereals, and much higher amounts of fiber and minerals than any other GF grain. It has a high amount of lysine, arginine, tryptophan, and sulfur-containing amino acids.^[20] Amaranth flour has already been used to enrich cereal-based foods, including GF pasta.^[21] Amaranth bread, which has higher levels of protein, fiber, and minerals, is acceptable for celiac patients.^[20] A mixture of popped and raw amaranth flour produces bread loaves with a higher specific volume and more homogeneous crumb than other kinds of GF bread.^[21]

Quinoa

Quinoa protein is rich in lysine, methionine, and cysteine. Thus, it is a good complement for legumes, which have low methionine and cysteine. In addition, quinoa is a relatively good source of Vitamin E and B-group vitamins and has high levels of calcium, iron, and phosphorous. It also has a suitable fatty acid composition.^[22] Dogan and Karwe demonstrated that quinoa could be used to make a novel, healthy, extruded snack product. Quinoa’s high lipid and low amylase contents make it necessary to have a high shear in extrusion cooking.^[23]

Buckwheat

Buckwheat seeds contain fagopyritols, a type of soluble carbohydrates. Fagopyritols are a source of D-chiro-inositol, a compound that has shown efficiency in patients with noninsulin-dependent diabetes through improved glycemic control. Buckwheat has a low glycemic index and also shows a beneficial effect on human health, lowering blood pressure and helping cholesterol metabolism.^[24] Replacement of

Table 1: Certain mineral content of pseudocereals

Seed	Ca	Mg	Zn	Fe
Amaranth	180.1±6.1	279.2±1.1	1.6±0.0	9.2±0.2
Quinoa	32.9±3.3	206.8±6.4	1.8±0.0	5.5±0.5
Buckwheat	60.4±3.3	203.4±8.8	1.0±0.0	4.7±0.1
Wheat	34.8±0.0	96.4±3.7	1.2±0.1	3.3±0.1

cornstarch with buckwheat flour in GF bread has been shown to have a positive effect on bread texture and delays staling because of buckwheat flour's lower starch gelatinization enthalpy.^[25] Utilization of buckwheat in the production of GF crackers leads to a product with acceptable sensory qualities.^[26] Buckwheat and quinoa breads have a higher volume than other kinds of GF breads.

Schoenlechner *et al.* compared different characteristics of amaranth, quinoa, and buckwheat pasta. They found that the firmness and cooking time of amaranth pasta was lower than those for the other flours, while the cooking loss of quinoa pasta was greater than other flours. Decreasing the moisture content to 30% and using higher amount of egg white powder and emulsifier (distilled monoglycerides) led to a firmness that was more acceptable than that for the wheat pasta.^[22]

Maize

Maize's high yields have made it a key crop in ensuring food availability and promoting food security.^[27] It is recommended as a safe source for the production of GF pasta. In addition, products such as curls, puffs, and balls can be produced by extrusion cooking of maize grits or meal, and fried snack products such as tortilla chips can be made from alkaline-processed maize. Breakfast cereals such as flakes, shreds, granules, puffs, or other forms can also be produced from maize.^[13]

Millet

One good source of nutrients, especially fiber, calcium, and other minerals, is millet.^[28] Protein makes up about 7%–12% of the grain. Lysine is a limiting amino acid in millet, while tryptophan and threonine are not deficient.^[9] The best-known flat breads produced from millet are injera, kiswa (fermented), and roti (unfermented). Injera made from millet stales much more slowly than that made from sorghum or other cereals. Teff is a kind of millet that has protein content similar to the other cereals (10%–12%) and is a good source of minerals, particularly calcium and iron. The main use of teff grain in human food is in injera.^[29] Teff starch has a slow retrogradation rate that delays bread staling.^[13,30] Millet's lysine deficiency can be overcome by blending it with a lysine-rich flour such as legume flours. Baby foods, snack foods,^[31] and breakfast cereals^[32] are other products made from millet. Germinated, popped, and roasted millet flours have been used along with milk solids, legume flour, and other cereals for the production of complementary and infant foods.^[33]

Sorghum

White, pleasant-tasting, and GF flour can be produced from sorghum.^[34] The nutrition quality of sorghum protein is poor, as sorghum is deficient in essential amino acids. Malting can increase lysine and improve protein quality.^[35]

Breads produced from sorghum have lower volume than wheat bread.^[36] For sorghum bread, soft batters rather than firmer dough are required to obtain sufficient rise and good elasticity without brittleness; thus, more water is generally required.^[34] In GF products, gas cells should be surrounded by liquid films and stabilized by surface-active substances such as polar lipids, soluble proteins, and soluble pentosans; these are present in sorghum, making it suitable for producing bread without any additives. However, using hydrocolloids could improve sorghum bread's quality.^[34] Various researchers have studied the effect of using different additives on sorghum bread quality. Some of these studies are presented in Table 2. Sorghum flours have also been used to produce biscuits, granolas, infant food, and snack foods such as crisps and chips.^[35,37]

Chestnut

Chestnut flour contains high-quality proteins with 4%–7% essential amino acids, 20%–32% sugar, 50%–60% starch, 4%–10% dietary fiber, 2%–4% fat, and some vitamins and minerals, such as B-group vitamins and Vitamin E, phosphorous, magnesium, and potassium. Since the amounts of Vitamin B, iron, folate, and dietary fiber are not sufficient in most GF flour, the use of chestnut flour seems to be advantageous for improving nutritional value. Unfortunately, the qualities of chestnut bread, such as volume and color, are not suitable because of weak interactions between components of the chestnut dough,^[1] inadequate starch gelatinization, and high amounts of sugar and fiber. This flour is more suitable for pastry making.^[38] However, blending chestnut flour with other flours such as rice flour^[38] and adding some hydrocolloids such as guar gum, xanthan gum, or hydroxypropyl methylcellulose (HPMC)^[1] can help to overcome these problems.

Chia flour

The chia (*Salvia hispanica* L.) seed and flour were one of the main staple foods in Central America. It attracts a great deal of interest due to its nutritional and functional potential in food and pharmaceutical industries. The chia seed is a good source of phenolic compounds, dietary fiber (20%–37%), protein (18%–25%), and oil (21%–33%) with approximately 60%–63% α -linolenic acid. Sandri *et al.* used chia flour, potato starch, and rice flour in a GF bread formulation by application of mixture design and response surface methodology to achieve the best sensory properties. They found no suitable physical and sensory properties when whole chia flour alone was used. After that, 5%, 10%, and 14% whole chia flour was added to GF bread-containing rice flour as a main ingredient that led to negligibly decrease in crumb moisture, crumb firmness, and loaf volume.^[39] Huerta *et al.* observed no significant differences in replacing rice and soy flour with 2.5%, 5.0%, and 7.5% whole chia flour in specific volume, baking loss, and sensory

acceptability (scores ranging from 4.5 to 5.5, on a 7-point hedonic scale) on GF bread in comparison to control.^[40] In another study, 2.5%–7.5% whole chia flour was used in chestnut flour-based GF bread formulation. They found improved in the dough rheological properties of elasticity, viscosity, and stability up to using 7.5% chia flour.^[41,42] Steffolani *et al.* found that replacing of rice flour with 15% whole chia flour reduced the specific volume, darkened the GFB color, and increased the bread hardness but does not have significant effect on overall acceptability.^[43]

Legumes

Breads produced from legumes such as pea isolate, chickpea flour, soya flour, or carob germ flour showed good sensory profiles and physicochemical characteristics. Carob germ flour produced batters with good rheological characteristics, but its bread had poor properties. However, chickpea flour and pea isolate kinds of bread obtained good results in all parameters.^[44] In another study, Gularte *et al.* made GF cake using chickpea, pea, lentil, and bean flours along with rice in a proportion of 50:50. Application of legume flours, especially lentil, led to lower batter viscosity and consequently higher specific volume than in the control sample. In addition, lentil-enriched cakes showed similar crumb hardness and higher springiness than the control cake. In terms of nutritional quality, legumes have a higher protein content and protein availability than cereals; this makes legumes as a recommended flour for enriching GF cakes.^[45] Tsatsaragkou *et al.* (2014) showed replacing 15% of rice flour with carob flour resulted in the production of GF bread with better crumb structure and color, and lower moisture loss but harder crumbs and lower specific volume than rice bread. The decrease in size of carob flour led to a slower rate of firming.^[46]

DIFFERENT CHALLENGES ENCOUNTERED IN USING GLUTEN-FREE FOOD

Cost

A comparison between GF commercial foods and their gluten-containing counterparts shows that GF food is more expensive.^[47] The price of one loaf of GF bread is two or three times that of regular bread. Activities such as baking celiac-specific cereal products, buying foods in large quantities with friends or support-group members, and choosing longer lasting products such as carrots, potatoes, and parsnips, seasonal products, and legumes could help patients to reduce food costs.^[48]

Nutritional deficiencies

Between 20% and 38% of celiac patients show nutritional deficiencies: 12%–69% display iron deficiency and 8%–41% display Vitamin B₁₂ deficiency. In addition, damaged villi in celiac patients lead to lactose intolerance because of decreased lactase production, resulting in phosphorus, calcium, and Vitamin D deficiencies.^[47]

Using starches and refined flours with low fiber content in GF products leads to inadequate fiber intake.^[47] The incidence of anemia in newly diagnosed celiac patients was reported as 4% in the United States. Gluten-containing products have higher folate content than their GF counterparts. Therefore, fortification of GF products with folate is essential.^[49] Immediately after diagnosis of a deficiency in these and other micronutrients, GF vitamins and minerals should be added to the patient's diet in therapeutic doses based on individual factors, including laboratory test results, age, overall eating habits, and compliance with the GFD.^[8] Patients should be encouraged to use foods rich in Vitamin B₁₂ (such as meat, milk, fish, and poultry), folate (such as dried beans and legumes, flax seeds, dark leafy greens, and citrus fruit), heme iron (such as lean meats, poultry, and seafood), and nonheme iron (such as legumes, seeds, and nuts), as well as vitamin C-rich food to increase iron absorption. Pseudocereals such as amaranth, buckwheat, and quinoa are good sources of iron, fiber, and some B vitamins.^[50]

Obesity

Recent studies showed a high prevalence of obesity in some celiac patients.^[51] Almost half of all adult patients with celiac disease have a body mass index of 25 or more;^[52] however, obesity is more prevalent in celiac children, and it is, therefore, necessary to test for celiac disease in obese children.^[52] Hyper caloric content of commercially available GF foods might be resulted to obesity and weight gain.^[53] Furthermore, damage of intestinal villi can lead to problems in food digestion and absorption that result in obesity.

Bone disease

Consumption of calcium-rich and Vitamin D-rich foods should be recommended throughout patients' lives, particularly those patients with osteopenic bone disease.^[54] Calcium-rich foods include milk, cheese, and calcium-fortified beverages such as orange or apple juice, and enriched, GF soy, almond, or rice milk, GF yogurt, sardines, or canned salmon with bones.^[55] Vitamin D-rich foods include fatty fish and fish oils, egg yolk, liver, Vitamin D-fortified milk, and some GF enriched beverages; additionally, patients should be encouraged to expose their skin to sunshine during late spring, summer, and early fall.

Lactose intolerance

A common problem for celiac is bloating, gas, and diarrhea; these may indicate lactose intolerance. Lactose consumption should be avoided and limited for one or more months in this situation until lactase enzyme production recovers. Different recommended strategies include using lactose-reduced or lactose-free products such as Lactaid® milk, aged cheese, and GF yogurt with live and active cultures, enriched dairy-free/GF beverages such as soy,

almond, or rice milk, and supplementation with GF lactase enzyme supplements.^[55]

Technological challenges

As mentioned before in detail, the quality, mouth-feel, and flavor of GF products are lower than those of conventional wheat products. The elasticity and extensibility of dough and the volume of the loaves are attributed to gluten.^[56] Cereal products baked with different GF cereals (with the exception of oats) have been shown to have lower volume and an inferior physical texture but a slower staling rate than wheat containing samples.^[57] Different additives, such as hydrocolloids, emulsifiers, starch, eggs, and other materials, have been used as improvers in the production of GF products. Some of these additives are discussed in [Table 2].

Hydrocolloids

Hydrocolloids can be applied as gluten substitutes in the production of GF food due to their polymeric structure.^[32] The properties of hydrocolloids used as gluten replacers, such as network forming, film formation, thickening, and water-holding capacity, are useful in the formulation of GF products. Guar gum and xanthan gum are the two most common hydrocolloids used in GF-baked products.^[9] Addition of xanthan to GF formulations leads to a farinograph curve typical of wheat flour dough.^[58] This gum has a positive effect on bread volume and leads to a product with a higher volume than do pectin and guar gum.^[59] Increased xanthan content reduces the hardness of bread.^[59] In addition, when xanthan gum was applied as a network former in the preparation of cornstarch bread, the resulting product had a good specific volume but a coarse crumb texture, without flavor.^[60]

HPMC is a cellulose derivative that has a positive effect on the reduction of cholesterol and has also been used in GF breads to increase loaf volume.^[61] The use of HPMC as a substitute for gluten ensures good gas-retaining and structure-forming properties in the crumb of rice bread.^[62] In fact, a comparative study using different gums (xanthan gum, guar gum, agar, carrageenan, locust bean gum, and HPMC) in a rice-bread formulation showed that HPMC gave the highest specific loaf volume.^[63] The cellulose carboxymethyl cellulose (CMC) has been used as a gluten replacer in the production of bread. CMC can increase the porosity and crumb elasticity of bread as well as the overall acceptability of a GF formulation.^[58] When this gum has been used for the production of rice-flour cake, better sensory properties in terms of uniformity, crust property, rupture, aroma, taste, and flavor were obtained in comparison with control rice-flour cake.^[64] Furthermore, an appropriate amount of CMC and HPMC improved rice-cracker texture.^[65]

Pectin,^[59] agarose,^[59] oat β -glucan,^[58] psyllium,^[66] Arabic gum,^[67] konjac,^[68] locust bean gum,^[56] agar-agar,^[69] and guar gum^[38] are other hydrocolloids that have improved the texture, rheology, appearance, sensory perceptions,

and general quality of GF formulations. Some authors have investigated the effect of mixture of hydrocolloids.^[70] Sumnu *et al.* studied the effects of different concentrations of xanthan and guar gums and their blends on the staling of GF rice cakes. They found that a blend of xanthan and guar gum decreased hardness, weight loss, enthalpy of retrogradation, and the change in setback viscosity values of cakes during storage, thus retarding staling.^[70] Using xanthan, CMC, xanthan-guar, xanthan-locust bean, and HPMC have been shown to yield the lowest porosity, the lowest average area of pores, and the highest number of pores; this, in turn, leads to a finer texture of these crumbs along with lower hardness and higher cohesiveness and springiness.^[38]

Starch plays a key role in the texture of many kinds of food products. In some cases, native starch does not provide the functional properties, such as thickening and stabilization, for the production of some special foods. Therefore, starches used in the food industry are often modified to overcome undesirable changes in product appearance and texture caused by retrogradation or breakdown of starch during processing and storage.^[71] The most widely used starches in the food industry are hydroxypropylated, acetylated, and cross-linked starches. Hydroxypropylated starch influences the viscoelastic properties of dough. One of the main factors that could modify the rheological properties of GF modified starch as a part of the dough is water-binding capacity. However, the application of hydroxypropylated starches has not been shown to have a significant impact on pasting characteristics.^[72] Hydroxypropyl distarch phosphate enhances the volume of GF loaves. This is accompanied by a decrease in average cell size and an increase in average cell number.^[73]

Acetylation of starch is an important substitution method used for thickening GF food products.^[15] Like hydroxypropylated starch, acetylated distarch adipate could enhance the volume of GF bread. Addition of modified starch causes a more elastic crumb structure. A slight decrease in the hardness and chewiness of the crumb was also observable on the day of baking.^[73] Application of acetylated starch in cake batter could increase batter viscosity, cake volume, and whiteness of crust.^[15] When high and stable viscosity is required in food, cross-linked starches are used as the thickener. Cross-linked starches play an important role in increasing shear resistance and providing viscous batter.^[74] Cross-linked cornstarch provides stronger and more stable dough and increases the loaf volume.^[75] The use of resistant starch has been shown to elevate zero-shear viscosity and reduce both creep and recovery compliance. Modified starch has shown higher starch gelatinization temperatures and lower viscosity. It has been found that loaves baked with a proportion of resistant starch had a softer crumb than the control sample.^[76] Hydrolysis of some proportions of starch into a low molecular weight using amylolytic enzymes is another method of starch

modification. The resulting modified starch, called maltodextrin or dextrin, significantly increases pasting temperature and reduces the viscosity of the obtained pastes. Maltodextrins can attenuate structure and increase deformation sensitivity. The addition of maltodextrins with low dextrose equivalent (DE) decreases loaf volume and causes the deterioration of bread quality. Maltodextrins with the higher DE positively influence bread volume and have a beneficial effect on crumb hardening during storage. Maltodextrin with the highest DE also effectively reduces the recrystallization enthalpy of amylopectin.^[77]

Protein

Phongthai and D'Amico (2017) studied the properties of rice-flour-based GF pasta enriched by whey protein concentrate (WP), egg albumen (EB), soy protein (SP) and rice bran protein concentrate, separately. Using WP caused decrease in optimal cooking time. The enrichment of 9% (w/w) EB led to prevent structure from disintegration, improved pasta firmness, and decrease in cooking loss of $P < 0.05$, whereas using rice bran protein concentrate caused highest cooking loss ($P < 0.05$). The GF pasta enrichment with 6% SP concentrate had similar L^* values in comparison with commercial sample. Among the four sources of protein tested, EB had the highest potential for improving cooking properties of rice-flour-based GF pasta.^[78]

In addition, application of modified protein could improve the quality of GF products. Deamidated oat protein has been shown to cause lower viscosity, a higher volume, and a darker color.^[15] The substitution of a combination of deamidated protein and acetylated starch could improve oat-flour cake properties.^[79]

Fiber

GF flour often tends to have reduced fiber compared with products containing gluten. Different fiber sources, such as cereal bran, legume outer layer, modified cellulose and resistant starch, and by-products of apple and potato processing, have been used in producing GF products. The replacement of 20% rice flour with a mixture of oat fiber and inulin in GF layer cakes has been shown to increase the cakes' specific volume and quality.^[45] The degree of polymerization of inulin and the proportion of low-molecular-weight sugars in the recipe could influence dough properties. The incorporation of inulin to dough formulations causes a significant decrease in paste viscosity and an increase in gelatinization temperature. Inulin significantly reduces the enthalpy of retrograded amylopectin, resulting in slower staling.^[80] Addition of rice bran containing a high amount of soluble dietary fiber produces better bread color, a higher specific volume, and softer crumb with a better porosity profile. Furthermore, sensory acceptance increases and shelf life extends in higher levels of soluble dietary fiber.^[81]

Dairy ingredient

The incorporation of dairy ingredients has long been established in the baking industry due to their nutritional and functional benefits, including improved flavor and texture and longer shelf life. Dairy products may be used as a gluten substitute to increase water absorption and enhance the handling properties of the batter.^[82] All powders derived from milk increase crumb hardness with the exception of demineralized whey powder. Sensory analysis has shown a preference for breads containing skim milk, sodium caseinate, and milk protein isolate.^[56] Other novel ingredients, such as calcium-fortified caseinate, were found to be suitable for gluten replacement, where calcium bonds in caseinate played the same role as sulfur-sulfur bonds in gluten.^[9] Another benefit of using dairy products is the doubling of the bread's protein content.^[56]

Enzymes

The enzyme transglutaminase (TGase) (EC 2.3.2.13) has been used in many industries, including dairy, bakery, and meat processing. TGase, a γ -glutamyltransferase, can catalyze the reaction between lysine residues (ϵ -amino group on protein bound) and glutamine residues (β -carboxamide group on protein bond), which cross-link proteins via covalent bonds, leading to the decrease in the number of free amino groups. TGase was found to have a severe effect on dough water absorption, modifying viscoelastic behavior and enhancing thermal stability.^[83] Furthermore, TGase has a significant effect on the specific volume of bread. Application of skim milk protein with 10 unit of enzyme has been shown to lead to the most compact structure, as reflected in the crumb texture profile. This could be due to the formation of a protein network in GF bread with the addition of TGase.^[84] Another enzyme that affects dough's rheological properties and bread's physical quality is protease. Protease-treated rice bread had better crumb appearance, high volume, soft texture, and slower staling rate, depending on the amount of enzyme added.^[85] The aggregation of partially degraded storage proteins surrounding the starch granules and protein-starch interaction may improve gas retention before baking and increase specific loaf volume.^[86] In another study, application of protease of *Aspergillus oryzae* on the rheological properties of rice dough showed an increase in batter viscosity and a decrease in flour-settling behavior because of the aggregation of flour particles after partial cleavage of storage proteins.^[86]

Sourdough

The use of sourdough represents an alternative to increase the quality of both gluten-containing and GF breads. Acidification of flour by sourdough fermentation can replace the function of gluten to some extent and enhance the swelling properties of polysaccharides, leading to a better bread structure. It also improves bread volume and crumb structure, flavor, nutritional value, and mold-free shelf life. Sourdough lactic acid bacteria could break down

nongluten proteins and starch components, thus increasing the dough elasticity and delaying staling.^[87] Furthermore, long-chain sugar polymers called exo-polysaccharides can be produced by many lactic acid bacteria and act as prebiotics and hydrocolloids to improve the technological as well as nutritional properties of GF breads.^[87] Rühmkorf *et al.* optimized homoexo-polysaccharide production by lactobacilli in GF sourdoughs to achieve high amounts of exo-polysaccharides.^[88] The complementary peptidases located in the cytoplasm of lactobacilli hydrolyze gluten and reduce its amount to <10 ppm through routine sourdough fermentation.^[89] On the other hand, the proteolytic system of lactic acid bacteria has the ability to hydrolyze α -gliadin fragments and reduce gliadin levels to some extent. Furthermore, the application of these peptidases seems to be a possible technological alternative to reduce the gliadin concentration in wheat dough without using living bacteria as a starter.^[90] Lactic acid bacteria can also produce antifungal, antimycotoxigenic, bioactive, and aroma compounds that have the ability to improve overall bread quality.^[87,91]

Other materials

So far, some studies have been conducted in this area using uncommon materials as gluten alternatives. For example, the study of replacing wheat flour with a mixture of GF flours and psyllium showed no change in the preference or acceptability of modified products compared with standard products. Healthful, tasty, and low-cost products could be made at home using this replacement.^[66] Another material, which contains high amounts of protein, dietary fiber, calcium, and ω -3 fatty acids, is the pulpy by-product of soy milk named okara. It can play an important role as a gluten substitute, which develops proper product texture, mouthfeel, and volume after some reformation. Okara has large amounts of fiber that interferes with protein-starch interactions. Decreasing the fiber size can overcome this problem. In addition, in comparison with a commercial GF flour in batter formulations, okara has been suggested as a novel marketable ingredient for the formulation of a variety of GF products.^[92]

Table 2: Different gluten substitute used in different gluten-free food

Kind of cereal flour	Gluten substitutes	GF product	Effect of using Gluten substitutes	References
Millet	Xanthan gum and guar gum	Bread		[13]
Sorghum	Methyl cellulose	Bread	Increasing gas retention-preventing loafs from collapsing	[37]
Sorghums	Isolated starch and methyl cellulose	Bread	Improving bread volume and crumb structure	[37]
Sorghum	α -amylases, proteases and emulsifiers	Bread	Weakening the crumb structure	[37]
Sorghum	Methyl cellulose and shortening	Bread	Softening the loaves	[37]
Sorghums	Comparing addition of xanthan gum, soya flour and corn starch	Bread	Increasing corn starch level lead to highest volume	[93]
Sorghum	Skim milk powder	Bread	Negative effect	[93]
Sorghum	Corn starch and pregelatinized starch	Bread	Improving bread quality	[38]
Sorghum	Rye pentosans	Bread	Increasing volume and delaying staling	[13]
Corn	Starch	Pasta	Improving pasta quality	[94]
Corn	Hydrocolloid and dairy proteins	Pasta	Improving mouth feel and shelf life	[94]
Corn and oat	CMC and chitosan	Spaghetti	Producing oat enriched pasta like unmodified corm pasta	[94]
Rice	Emulsifier (DATEM), xanthan, gum, guar gum, LBG, hydroxypropyl methylcellulose, pectin, xanthan guar, xanthan-LBG	Bread	Emulsifiers and xanthan guar and xanthan-LBG caused to the best firmness and specific volume values	[38]
Rice	κ -carrageenan and carboxymethyl cellulose gums combined with SSL	Bread	Delaying staling	[95]
Rice	Emulsifier	Pasta	Improving cooking properties, decreasing cooking loss	[96]
Rice	Cross-linked starch and monoglyceride	Pasta	Improving stickiness	[96]
Rice	Heat moisture treatment flour	Noodle	Improving flavor, firmness, adhesiveness, and total acceptance	[97]
Rice	Xanthan gum and guar gum	Cake	Retarding staling	[70]
Rice		Flake, cracker		[13]
Oat	Hydrostatic pressure treatment	Bread	Increasing elasticity of oat dough because of increased gelatinization of oat starch and protein network formation, lead to fresher bread	[98]
Maize-buckwheat blended flour		Bread	Improving chewiness and gumminess, without effect on volume	[82]

CMC=Carboxymethyl cellulose; SSL=Sodium stearyl-2-lactylate; LBG=Locust bean gum; GF=Gluten free; DATEM=Diacyl tartaric acid ester of mono- and diglyceride

NUTRIGENOMICS

As mentioned above, the traditional concept of celiac disease is a chronic inflammatory disorder that identified by malabsorption in human.^[93,99] Although celiac disease is treatable by the total lifelong GFD,^[94,100] due to mentioned problems, the use of other controlling methods can delay symptoms. Nutrigenomics can be used as a new method for celiac disease control. Nutrigenomics and nutrigenetics are two research fields that elucidate some interactions between diet, nutrients, and genes. Nutrigenomics studies the functional interactions of food with the genome. Some food ingredients such as plant flavonoids, carotenoids, and long-chain ω -3 fatty acids can modulate oxidative stress, gene expression, and production of inflammatory mediators; this modulation activity can preserve the integrity of the intestinal barrier and protect against the toxicity of gliadin peptides; thus, these ingredients can be used in nutritional therapy for celiac disease.^[93] Vitamins C and E can modulate immune responses in several ways, such as via leukocyte function and lymphocyte proliferation. They have also antioxidant activity that leads to modulations of the inflammatory process. Vitamin E, especially γ -tocopherol, decreases the release of the pro-inflammatory cytokines IL-8 and PAI-1. In addition, Vitamin C can inhibit the augmented secretion of interferon-gamma, tumor necrosis factor-alpha, and IL-6 and increase the expression of IL-15 triggered by gliadin; this is beneficial in the treatment of celiac disease.^[101] Other effective compounds on the intestinal epithelial cells are several polyphenols and carotenoids found in fruit and vegetables that have antioxidant and anti-inflammatory properties. Flavonoids reduce the concentration of prostanoids and leukotrienes through inhibiting the activity of eicosanoid-generating enzymes such as phospholipase A₂ and preventing the induction and expression of inducible nitric oxide synthase in different cell models. In addition, carotenoids can inhibit the expression of enzymes/proteins that play a role in inflammation, partly by suppressing the activation of the transcription factor NF- κ B. Other flavonoids such as lycopene, quercetin, tyrosol, epigallocatechin, gallate, genistein, and myricetin also have a protective effect on intestinal-barrier function. On the other hand, fatty acids can act via cell-surface and intracellular receptors/sensors that control inflammatory cell signaling and gene expression patterns. Although eicosanoids produced from ω -6 fatty acids (such as arachidonic acid) have a pro-inflammatory role, eicosanoids from ω -3 fatty acids (such as eicosapentaenoic acid) have anti-inflammatory properties. It has been presented that the release of arachidonic acid from intra-epithelial lymphocytes after incubation with gliadin leads to the activation of cytosolic phospholipase A2 cPLA2, which results in the lymphocyte cytolysis and immune response of celiac disease. Furthermore, it has been shown that

docosahexaenoic acid, as a long chain ω -3 polyunsaturated fatty acid, can disturb the pro-inflammatory effects of arachidonic acid.^[93,101]

CONCLUSION

Celiac patients usually need to adhere to a strictly GFD for the rest of their lives. Different GF cereals and additives have been used in GF products; the additives contribute structure-building and water-binding properties to GF-baked goods. The comparison between previous studies showed that pseudocereals and legumes are appropriate choices for making GF products because of their significantly higher levels of protein, fat, fiber, and minerals. From an economic perspective, pseudocereals offer a cheaper alternative to wheat that can help increase dietary compliance by reducing the economic pressure of a GFD. Each method for the production of GF food suffers from limitations, such as nutrition deficiency or deterioration of functional properties. As a result, the unpalatability and weak functional properties must overcome while maintaining nutritional value and safety.

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Conflicts of interest

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