Abstract

Mankind has long been aware of the advantages of plants in preventing diseases. Recipes for functional foods, medicines, and nutritional supplements are made using preparations from these sources. Over generations, a sedentary lifestyle and irregular eating habits have brought a negative impact on an individual's dietary choices and well-being. This led to the onset of diseases such as diabetes, obesity, hypertension, stroke, celiac and asthma. Amongst these, the disease that has gained much attention is celiac. It is an autoimmune disease characterized by an adverse reaction to gluten, a protein found in wheat, barley, and rye. People with gluten intolerance avoid foods that cause intolerance. Through the decades, the incidence of celiac disease (CD) has increased by approximately 7.5% per year worldwide, with a higher proportion of the affected population being female. This has led to the exploration of resources suitable for such a population to meet their nutritional requirements. Consequently, there is a growing tendency in research that focuses on the use of alternative grains that may be healthful to develop gluten-free products. Pseudocereals are increasingly being recognized for a gluten-free diet (GFD) due to their high nutritional content. In addition, they are also rich in vitamins and minerals. Similarly, amaranth is also a pseudocereal and currently generating more scientific and commercial interest due to its phytochemical profile containing essential minerals like iron, magnesium, phosphorus, bioactive compounds, protein, dietary fiber and antioxidants like vitamin E, valuable biological properties, and pharmaceutical properties. Its nutritional properties are equivalent to those of other ordinary grains considering the composition of crude protein, crude fat, carbohydrates (starch), and fibre. Therefore, this versatile grain can be integrated into daily dietary preferences to cater the issue of gluten-intolerance being a hindrance in obtaining required nutritional intake in day-to-day life of celiac patients.

Keywords

Amaranthus cruentus, Antioxidants, Pseudocereals

Introduction

CD is an autoimmune condition that results in intestinal mucosal injury caused by dietary exposure to gluten in individuals who are genetically susceptible. Gluten is a protein found in wheat, barley, and rye, and ingestion of this protein triggers an autoimmune response in individuals with CD. This leads to inflammation in the small intestine, specifically the duodenum, and damages the villi, which are tiny finger-like projections responsible for absorption of nutrients [1, 2]. The sole option for treating CD is strict adherence to a GFD. However, patients frequently encounter difficulties in maintaining this diet and selecting appropriate nourishing foods. This dietary regimen may lead to imbalances in nutritional intake, either deficiencies or excesses [2-4]. Hence it leads to the intro-
duction of pseudocereals. Pseudocereals are a class of naturally gluten-free, non-grass plants that can lessen these restrictions and improve the GFD.

Meta-analysis of the incidence of CD was done based on geographic regions, age groups and its prevalence in the time in which different studies were conducted. It was found that the collective occurrence of CD globally, as cited between January 2011 and March 2016, was 0.8%, indicating a surge in the prevalence of CD over time. The increased incidence is significant, considering the pooled female incidence at 17.4 per 100,000 person-years compared to 7.8 in males. In South America, the incidence of CD was 0.4%, while in Europe and Oceania, it was 0.8% [5]. This is most likely due to genetic factors and environmental factors like wheat consumption routine, age at which wheat is introduced, infant feeding practices, gastrointestinal infection history and rates of cesarean sections. Africa had the lowest zero-prevalence of CD (1.1%), and Asia had the highest (1.8%) [6]. Table 1 represents the approximate incidence of CD in different countries in different time periods.

To curb the global burden pertaining to the disease and introducing more CD friendly diets, studies on the less consumed food sources are required. Pseudocereals can prove to be promising food groups which celiac patients can lead to providing them with rich nutritional and health benefits. Amaranth is one such pseudocereal that has gained increased attention from the food industry and researchers in recent times owing to its versatility in different domains like healthy food alternatives, vast health benefits and industrial applications. One of its characteristics that needs to be highlighted is its gluten-free nature making it suitable for celiac patients. There has been a rise in the cases of weakened immune system due to sedentary lifestyle and genetic heredity. In 2005, the World Health Organization provided an estimate indicating 35 million deaths, which accounted for 61% of the total, with 49% of the global disease burden linked to chronic illnesses or lifestyle diseases. It was projected that by 2030, the percentage of worldwide deaths caused by chronic diseases would likely rise to 70%, with the global disease burden increasing to 56%. This increase is anticipated to be most significant in the African and Eastern Mediterranean regions. The shift in lifestyle has also led to occurrence of autoimmune diseases, one of which is gluten intolerance or CD. This has driven the food industry to expand their resources to formulate novel products for the ease of such population. These product formulations include gluten-free bread from flaxseed oil cake extract [7], gluten-free bread from rapeseed protein isolate [8], pasta from buckwheat flour [9], etc. Several nature derived gluten-free resources like quinoa, buckwheat, flax, millet, bajra have been explored including amaranth. It is a grain classified as pseudocereal that has been long existing in dietary history worldwide. In addition to the high nutritional value of seeds and leaves [10], it is easy to cultivate owing to its pests, drought and salinity resisting nature [11].

In recent years, it has been used in different forms such as flour obtained from seeds. Blended with wheat flour, it can increase the nutritional aspect of products like cakes, breaks, cookies, noodles. Starch isolated from amaranth can potentially be used as thickening agent. Other amaranth based products mainly consumed in Asia and South America are the candied and snack-based products. In Eastern Asia, as well as in countries like India and China, some species of Amaranthus are used in curries and soups. In Africa, the plant is utilized to enhance nutrient uptake. In addition to its gluten-free property, its nutritive qualities considering the levels of crude protein, crude fat, carbohydrates (Starch) and fiber make it comparable to other conventional grains. This property of amaranth provides an opportunity to replace major grains in case of shortage and deficiency of essential nutrients [12]. The edible stems and leaves of many Amaranthus species provide dietary fiber, vitamins, carotenoids, minerals, and high protein including lysine and methionine. Moreover, it has naturally occurred phytochemicals like phenolic acids and flavonoids. Its leaves contain significant amounts of vitamins (A and C), calcium, and folate, as well as polyphenols, saponins, tannins, and oxalates [13]. There are number of flavonoids and phe-noolic acids extracted from Amaranthus, such as, vanillic acid, gallic acid, p-hydroxybenzoic acid, syringic acid, trans-cinnamic acid, ferulic acid, rutin, catechin, quercitin, hyperoside, myricetin, isoqueretin etc. [14]. It belongs to the family Amaranthaceae, and includes almost 60 species, out of which three are used for cultivating commercially i.e., A. hypochondriacus, A. cruentus, and A. caudatus [15]. But some of its species like A. retroflexus, A. viridis, and A. spinosum non-edible [16].

The future of the gluten-free cereal market looks promising as consumer demand continues to grow. With an increasing number of individuals being diagnosed with CD and others choosing to eliminate gluten from their diets for various reasons, the demand for gluten-free cereal products is expected to rise. Therefore, amaranth being gluten free and having rich nutritious profile leads to promising health benefits therefore make the conscious choice to remove gluten from the diets of gluten intolerant people.

### Health Benefits

Amaranth has a rich nutritious profile, such as vitamins B, C and E, lipids, mineral (magnesium, calcium, copper, phos-

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**Table 1: Meta-analysis of CD.**

<table>
<thead>
<tr>
<th>Country</th>
<th>Period of study</th>
<th>Age group</th>
<th>Incidence</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>2000-2001</td>
<td>Adults</td>
<td>1.33±</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td>2004-2006</td>
<td>Adults</td>
<td>39.3±</td>
<td>[6]</td>
</tr>
<tr>
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<td>2005-2010</td>
<td>Children</td>
<td>2.60±</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1972-2009</td>
<td>Children</td>
<td>25.9±</td>
<td></td>
</tr>
<tr>
<td>United Kingdom</td>
<td>2000-2002</td>
<td>Not stated</td>
<td>0.6±</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1990-2011</td>
<td>Adults</td>
<td>14.6±</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>2009-2012 (Maracena)</td>
<td>Children</td>
<td>3.03±</td>
<td></td>
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<tr>
<td></td>
<td>2006-2007 (Nationwide)</td>
<td>Children</td>
<td>54.0±</td>
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<tr>
<td>Netherlands</td>
<td>1997-1998</td>
<td>Children</td>
<td>0.51±</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1995-2010</td>
<td>Children</td>
<td>8.2±</td>
<td></td>
</tr>
<tr>
<td>Estonia</td>
<td>1998-1999</td>
<td>Children</td>
<td>0.34±</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1976-2010</td>
<td>Children</td>
<td>1.1±</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Incidence reported in percentage (affected population/total test population). 2. Incidence per 1,00,000 people.
A Systemic Review and Meta-analysis of a Traditional Pseudocereal - Amaranthus cruentus

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Phosphorus, zinc iron and manganese), proteins and dietary fiber. In addition, it also contains bioactive phytochemicals like carotenoids, betanin's and phenolics and has been reported by Sarker and Oba [14]. These constituents have proven to be collectively responsible for the following health benefits (Figure 1).

Anti-diabetic effect

Diabetes is a growing concern in the current population. While type 2 diabetes involves a complicated interaction of factors causing insulin resistance, decreased insulin production and high blood glucose levels, type 1 diabetes results from an autoimmune reaction that targets the insulin-producing beta cells within the pancreatic islets of langerhans. Diet plays an important role in managing disease by regulating blood glucose levels, prevent complications, and support overall health. Amaranth seeds are enriched with essential nutrients and bioactive compounds, making them a promising therapeutic agent. Compounds like flavonoids and polyphenols found in seeds may enhance insulin sensitivity and regulate glucose metabolism, making a significant contribution to diabetes management [17]. A study done by Kim et al. [18] examined the anti-diabetic and antioxidant effects of amaranth grain (AG) and its oil fraction (AO) in streptozotocin-induced diabetic rats. The rats were divided into four groups: normal control, diabetic control, diabetic-AG supplement, and diabetic-AO supplement. The results showed that AG and AO supplement significantly decreased serum glucose and increased insulin levels in diabetic rats. The serum concentration of liver function marker enzymes was normalized by AG and AO treatment. AG and AO supplement normalized antioxidant enzyme activities, suggesting that AG and AO supplement may be beneficial for correcting hyperglycaemia and preventing diabetic complications.

A study on amaranth (A. hypochondriacus) was done by Velarde-Salcedo et al. [19] to observe the effects of DPPIV (Dipeptidyl Peptidase IV) inhibition on the "incretin effect." The incretin effect involves the production of incretins that enhance blood glucose regulation. These peptides have been known to have the ability to imitate the incretin effect and control blood sugar levels through stimulated gastrointestinal digestion. The raw amaranth flour demonstrated significantly higher DPPIV inhibition, highlighting its potential as a functional food element for glycemic control. It contains peptides from different protein fractions.

In another study, researchers investigated the anti-diabetic properties of an A. caudatus hydroethanolic extract containing mainly sugars, along with traces of polyphenols and amino acids. They tested it on type 2 diabetic Goto-kakizaki (GK) rats and healthy Wistar rats (Figure 2). It was found that during oral glucose tolerance tests a single oral dose of A. caudatus extract (2000 mg/kg) increased glucose tolerance in both the groups. Following A. caudatus therapy, HbA1c levels decreased in GK (19.83%) and Wistar rats (10.7%). Both GK and Wistar rats had elevated serum insulin levels, which were further confirmed in isolated pancreatic islets, where prolonged A. caudatus treatment boosted the synthesis of insulin. At 50 mg/ml, the effects of A. caudatus extract on in vitro glucose-dependent insulin production were concentration-dependent, resulting in up to an 8.5-fold increase in GK rat islets and a 5.7-fold rise in Wistar islets. When exposed to A. caudatus extract, perfused GK and Wistar islets significantly secreted more insulin (31-fold and 9-fold, respectively) [20].

Hypocholesterolemic activity

High blood cholesterol level is a pertinent risk factor for cardiovascular illnesses, which continues to be the leading cause of death worldwide. The application of natural dietary therapies that can lower cholesterol and the risk of heart disease has therefore sparked an increase in interest.

Figure 1: Various health benefits of amaranth.

Figure 2: Mechanism of effect of A. caudatus on insulin secretion studied by Zambrana et al. [20].
Hypcholesterolemic activity is the ability of certain substances or compounds to lower the levels of cholesterol in the bloodstream. The effects of substances that lower cholesterol are caused by several processes. One common mechanism includes preventing dietary cholesterol from being absorbed from the intestines, hence limiting its absorption into the bloodstream. Soluble fiber plays a role in reducing cholesterol levels by binding to cholesterol in the digestive tract, preventing its absorption into the bloodstream and promoting its elimination from the body [21]. Amaranth, being rich in dietary fiber, plays a pivotal role in lowering cholesterol level. The seeds also contain sterols, that are compounds structurally like cholesterol and therefore interfere with cholesterol absorption. Further, bioactive peptides found in amaranth also contribute to regulation of cholesterol by inhibiting the activity of enzymes involved in cholesterol synthesis [22].

A study conducted by Mendonça et al. [23] aimed to understand the mechanisms underlying the effects of amaranth protein in decreasing cholesterol. Male hamsters were fed a casein-rich diet with regular cholesterol levels for three weeks to cause hypercholesterolemia. The animals were split into three groups and fed diets containing casein (the control group), amaranth protein isolate, or a mixture of casein and amaranth protein isolate as their main source of protein for four weeks. The levels of cholesterol and triglycerides in their plasma were assessed at four distinct time points—at the start of the trial, following the induction of hypercholesterolemia, throughout the first week, and at the conclusion of the experimental diet period, With a p-value of less than 0.05, amaranth protein alone was very successful in considerably lowering plasma concentrations of different cholesterol components, such as total cholesterol, High-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, and triacylglycerols. Total plasma cholesterol was decreased by 48% when hamsters were fed diets containing only amaranth protein. It was reduced to 27% when casein and amaranth protein were mixed. Similar decreases were seen for non-HDL cholesterol, which were 39% when paired with casein and 57% with only amaranth protein. The reduced total/HDL cholesterol ratio was the possibility of amaranth protein being beneficial for lipid metabolism and lowering cholesterol levels.

Ajayi et al. [24] studied the cholesterol esterase (CEase) and pancreatic lipase (PL) inhibitory activities of amaranth protein hydrolysates (APHs) because these enzymes are often associated with occurrence of this disorder. In the intestinal lumen, CEase converts long-chain fatty acid esters of cholesterol into cholesterol and free fatty acids. Since cholesterol esters can’t be directly absorbed by intestinal epithelial cells, this step is crucial for the absorption of cholesterol. Inhibiting CEase is essential for managing hypercholesterolemia by reducing the generation and absorption of cholesterol. Another essential enzyme that plays a role in the digestion and absorption of lipids in the stomach is pancreatic lipase. Pancreatic lipase Inhibitors have been found to restrict the absorption of dietary fats because they hydrolyze triacylglycerols. These inhibitors have generated increasing interest for anti-obesity medications since they have proven useful in managing hyperlipidemia. APHs were obtained using bromelain, chymotrypsin, and actinase E at different time durations. When compared to chymotrypsin and actinase E hydrolysates, bromelain derived APHs led to the strongest inhibition of CEase and PL. Additionally, the IC50 values for all three enzymes reduced as the hydrolysis time increased, demonstrating that the rise in PL inhibitory activity is directly proportional to the lengthening of the hydrolysis time.

Anti-pyretic activity

The seeds’ nutritional composition, rich in essential nutrients, positions them as potential agents to alleviate fever-induced distress. Bioactive compounds offer relief from the challenges associated with fever. Clinical studies and experimental research reveal the potential anti-pyretic effects of amaranth seeds influencing temperature regulation and mitigating fever-related symptoms. A complex range of physiological responses, including fever, are brought on by both infectious and non-infectious sources. It involves an increase in body temperature, which is caused by a spike in prostaglandin E2 (PGE2) levels in particular brain regions. The activity of neurons in the hypothalamus that control body temperature is altered by this rise in PGE2 levels [25]. In a study, ethanolic extract of A. spinosus (EEAS) and methanolic extract of A. spinosus (MEAS) at doses of 200 mg/kg and 400 mg/kg were examined for any potential analgesic, anti-inflammatory, and antipyretic effects. MEAS had no noticeable effects at 200 mg/kg, but rats’ writhing was reduced by 11.06%. MEAS, however, had mild but substantial benefits at 400 mg/kg, which led to a 23.17% decrease in rat writing. In this trial, the reference medication diclofenac sodium (at 10 mg/kg) successfully reduced writhing in rats by 72.32%. Furthermore, the time it took for rats to respond to the hot plate stimulation was delayed in a dose-dependent way by both the extracts (EEAS and MEAS) and diclofenac sodium (10 mg/kg) [26]. Another study by Kumar et al. [27] studied antipyretic potential of methanolic extract of A. viridus (MEAV) was assessed using a method involving Brewer’s yeast-induced fever in rats. By administering a 20 ml/kg subcutaneous dose of a 20% aqueous brewer’s yeast solution in normal saline, fever was generated. MEAV was given orally in dosages of 200 mg/kg and 400 mg/kg, while paracetamol (provided orally in doses of 150 mg/kg) served as the reference medication and distilled water was supplied to the control group. The outcomes showed that at all tested doses, MEAV had considerable antipyretic efficacy. To be more precise, the 400 mg/kg dose of MEAV showed antipyretic effects that began 19 h after Brewer’s yeast administration and persisted until the end of the experiment.

Antimicrobial activity

In the world of medicine, antimicrobial activity has been essential in battling infectious disorders and enhancing general health. Antimicrobial drugs function in a variety of ways, such as by altering the composition of microbial cell walls, obstructing crucial metabolic processes, or focusing on proteins that are required for microbial survival. However, overuse and abuse of antibiotics have resulted in the development of antibiotic-resistant bacterial strains throughout time, posing a serious threat to global health. Due to the challenges faced by drug-resistant microorganisms, research into novel antimicrobial agents has increased, including the investigation of natural substances or compounds.
products. Among these, plant extracts have long been known to have antibacterial capabilities, making them a prospective treatment option for a variety of infectious disorders. These extracts, which come from a wide variety of plant species, contain many bioactive substances, including essential oils, alkaloids, flavonoids, and phenolics, which have strong antibacterial activities [28].

Due to its abundant concentration of phytochemicals, amaranth stands out as a prospective contender among the wide variety of plants. Many of the species of the diverse genus *Amaranthus* have been historically eaten as nutrient-rich meals all throughout the world. Amaranth has demonstrated the ability to combat microbial dangers in addition to its nutritional benefits. Many studies have been conducted to prove antimicrobial activity possessed by amaranth. The goal of one of the studies was to investigate the microorganism inhibiting abilities of a crude extract from *A. tricolor* (ATCE), as well as its potential use in the preservation of cooked meat. Using techniques such disc diffusion, calculating the minimum inhibitory concentration, and monitoring the growth curve, the research assessed the antibacterial efficacy against *Staphylococcus aureus*. The study also looked at modifications in intracellular pH, bacterial membrane potential, bacterial protein and DNA content, and cell shape to better understand how ATCE combats bacteria. Additionally, it was evaluated how different ATCE concentrations affected the pH, the color, and the bacterial counts of lean cooked pork during a 6-day storage period. The results showed that ATCE had an inhibition zone against *S. aureus* that ranged in diameter from 12.63 ± 0.34 to 12.94 ± 0.43 mm, and its minimum inhibitory concentration was found to be 80 mg/ml. The mode of action of ATCE against *S. aureus* includes several events, such as lowering of the internal pHi, depolarization of the cell membrane, reduction in bacterial protein content, cytoplasm leakage and DNA fragmentation within the cells. Furthermore, ATCE led to a reduction of 1.02 log CFU/g from a starting count of 3 log CFU/g when used on lean cooked pork contaminated with *S. aureus* [29].

Another study showed antibacterial activity of *A. viridis* extracts using various solvents like ethanol, petroleum ether, and water. The ethanol extract showed the highest efficacy against numerous harmful bacteria. Regarding *Klebsiella pneumoniae* (16 mm), *Proteus mirabilis* (16 mm), *Pseudomonas aeruginosa* (15 mm), and *Escherichia coli* (14 mm), it showed the largest inhibitory zones; *S. aureus* (6 mm) had the smallest. Petroleum ether extract had the strongest effects on *P. mirabilis* (16 mm), *K. pneumoniae* (19 mm), and *E. coli* (15 mm), but it had less of an impact on *P. aeruginosa* (8 mm) and *S. aureus* (7 mm). The aqueous extract of *A. viridis*, on the other hand, showed inhibitory zones against *K. Pneumoniae* (10 mm), *P. aeruginosa* (10 mm), and *E. coli* (9 mm) with reduced activity seen against *S. aureus* (8 mm) and *P. mirabilis* (8 mm). Maximum inhibition was seen against *K. pneumoniae* and *P. mirabilis* in all three solvent extracts of *A. viridis*, especially in the petroleum ether and ethanol extracts. *S. aureus* showed the smallest inhibitory zone, especially in the ethanol extract [30].

Also *A. spinosus* showed that it can stop the growth of both fungus and bacteria. This shows that *A. spinosus* might be used as an alternative to traditional synthetic drugs for treating topical wounds. Its antioxidant and antibacterial characteristics can be credited for its beneficial effects on different phases of the healing process [31].

**Antioxidant effect**

Antioxidants are essential for protecting our bodies from the damaging effects of oxidative stress, which results from an imbalance between free radicals with unpaired electrons and antioxidants. The body uses antioxidants as a line of defense against this oxidative damage and they can be found in a wide variety of foods including fruits, vegetables, nuts, and some spices. By giving unstable free radicals electrons, they stabilize them and stop them from harming cells and tissues. Plant substances with high antioxidant capacity include curcumin from turmeric, resveratrol from grapes, and green tea polyphenols. These help in scavenging dangerous free radicals, lowering oxidative stress and the threats it pose to health. In addition to promoting cellular health, their capacity to scavenge free radicals, aids in the prevention of chronic illnesses including cancer and heart disease. Amaranth has a high antioxidant capacity due to the presence of polyphenols, flavonoids, and carotenoids. It is an excellent source of zinc and manganese, two minerals that are necessary cofactors for several antioxidant enzymes in the body. These elements are essential for boosting the antioxidant defense mechanism. The phenolic content of amaranth seeds and their functional and bioactive qualities have attracted a lot of attention in recent years. The significance of phenolic chemicals in amaranth leaves and parts of the plant, however, has been brought to light by recent discoveries. The leaves, flowers, and stalks of amaranth include hydroxycinnamic acids, benzoic acids, flavonoids, and their glycosides. Furthermore, it was shown that young amaranth plants have an excess of hydroxycinnamyl amides. Amaranth leaf extracts have been shown to contain phenolics that have antioxidant potential by preventing the generation of nitric oxide and scavenging free radicals. The betalains, the betacyanins, are a different class of phytochemicals with antioxidant capabilities that are present in amaranth. A study evaluated the antioxidant capability, total phenolic content, and particular phenolic compounds in *A. caudatus* at various growth stages. The objectives of the study were to determine the exact growth stage at which the plant exhibits its highest antioxidant capacities and ways to use it as an antioxidant source for food production. Among the 17 different compounds found, rutin was the most prominent across all stages. Highest levels of flavonols and hydroxycinnamic acid derivatives were found in early blooming phases and vegetative phases respectively. In general, the antioxidant activity was lowest throughout the shooting and budding periods. The earlier (vegetative) and later stages of amaranth plants, on the other hand, showed significantly greater antioxidant activity levels, indicating that these stages offer rich sources of antioxidants [32].

**Effect against hypertension**

High blood pressure, or hypertension, increases the chance of developing cardiovascular problems. To control hypertension, a common approach is to inhibit the elements
involved in renin-angiotensin-aldosterone system. Pharmaceutical companies have created a variety of drugs that work against this pathway. These medicines include ACE and renin inhibitors, alpha and beta blockers, calcium channel blockers, vasodilators, and diuretics, as well as angiotensin II type-1 receptor (AT1 receptor) and ACE and renin inhibitors. Another alternative strategy, gaining attention, is the use of dietary treatments, specifically the consumption of functional foods. Bioactive peptides have been proven to have potential involvement in controlling blood pressure. Functional foods comprise a variety of ingredients known for their functional or physiological effects [33]. Cookies made from an alcalase-produced amaranth hydrolyzate were tested for their technical qualities and their capacity to decrease blood pressure. Male spontaneously hypertensive rats and female Balb/c mice were employed in the antihypertensive evaluations and bioavailability tests, respectively. Twenty-eight hypertensive rats were separated into four groups; the first group received cookies supplemented with amaranth hydrolyzate; the second received standard cookies; the third received an ACE-I inhibitor (captopril); and the fourth group simply received water. Various time periods were used to test blood pressure.

As a result of consuming cookies enriched with amaranth hydrolyzate, mice’s serum samples were found to inhibit ACE-1 activity from the initial evaluation at 5 minutes to the last evaluation at 120 min. Like this, captopril–treated mice serum samples suppressed ACE-1 activity for up to 60 min. After three hours of therapy, hypertensive rats that consumed cookies enriched with amaranth hydrolyzate had considerably lower blood pressure than those who consumed water or regular cookies. An interesting finding was that the amaranth-hydrolyzate-enriched cookies and Captopril both exhibited anti-hypertensive effects [34].

Mechanism of CD and its preventive measures

CD

CD is an immune-mediated systemic disorder triggered by gluten consumption, occurring in genetically predisposed individuals. Gluten refers to insoluble cereal proteins, including prolams found in wheat (gliadins), rye (secalins), barley (hordein), and oats (avenins). CD is a condition that develops due to a specific genetic background, primarily involving the presence of HLA-DQ2/DQ8 genes, along with other non-HLA genes. Environmental factors like viral infections and disruptions in gut microbiota also play a role in its development. This disease affects about 1% of the general population, with a higher incidence among females. It can manifest at any age and presents with a wide range of symptoms and variations, including gastrointestinal, subclinical, potential, seronegative, non-responsive, and refractory forms. Currently, the only effective treatment for CD is a lifelong, strict GFD. This dietary approach improves the quality of life for individuals with CD, alleviates symptoms, and reduces the risk of complications like refractory CD, ulcerative jejunoileitis, and small intestinal adenocarcinoma and lymphoma was reported by Houmich and Admou [1] and Tye-Din et al. [35].

Mechanism

CD is primarily driven by inappropriate immune response to certain components of gluten. Specifically, prolamins contain crucial segments recognized by HLA-DQ2 or HLA-DQ8, which then activate CD4+ T-lymphocytes. In the context of CD development, the role of the intestinal epithelial barrier is vital. Normally, this barrier prevents the passage of large molecules like gliadin. However, in individuals genetically predisposed to CD, gliadin interacts with intestinal cells, causing the breakdown of tight junctions between these cells. This disruption leads to an increase in zonulin, a peptide that regulates tight junctions and results in greater intestinal permeability. Gliadin fragments can then cross the epithelial barrier and activate T-lymphocytes in the lamina propria. These activated CD4+ T-lymphocytes produce pro-inflammatory cytokines, leading to either a T-helper 1 response dominated by IFN-γ or a T-helper 2 response, which promotes the clonal expansion of B-lymphocytes. These B-lymphocytes ultimately mature into plasma cells that produce antibodies against gliadin and tissue transglutaminase. Additionally, certain gliadin peptides that aren’t recognized by T-lymphocytes can stimulate antigen-presenting cells and intestinal epithelial cells. CD8+ T-lymphocytes may be activated through interleukin-15. An increased presence of CD8+ intraepithelial cells is a characteristic feature of CD (Figure 3). Tissue transglutaminase, an enzyme located either in the extracellular space beneath the epithelial layer or at the brush border of epithelial cells, has been found to enhance gliadin-specific T-cell responses, this has been reported by Houmich and Admou [1] and Tye-Din et al. [35].

Prevention

The occurrence and frequency of CD have increased over time. This is because of increased awareness and development of more accurate serological tests. The way CD presents clinically has significantly changed in recent decades. Patients who experience typical symptoms often face delays in receiving a CD diagnosis that can last for years, or even worse, go unrecognized and untreated. This is because of variable symp-
toms such as mal-absorption which leads to chronic diarrhea, impaired growth in children, abdominal swelling, weight loss, as well as general signs and symptoms like fatigue, osteoporo-
sis, or iron-deficiency anemia. Additionally, extra-intestinal symptoms like arthritis or neurologic manifestations are also commonly observed. Prevention would be advantageous as the burden of morbidity and death related to untreated CD is lessened when a GFD is followed (Table 2).

Primary prevention methods

Primary prevention of CD involves the acquisition of gluten tolerance because individuals with CD do not naturally develop it or regain it at a later stage in life [3, 4].

Secondary prevention method

Detecting and treating CD at an early stage is considered a form of secondary prevention. There are two distinct methods to accomplish this: case finding and mass screening [3, 4].

Tertiary prevention method

Tertiary prevention aims to minimize the consequences of an already existing illness through enhanced treatment methods. Gluten-containing grains like wheat, barley, and rye are significant sources of essential nutrients such as iron, calcium, folate, and vitamin B12. Since the treatment of CD with a GFD can lead to nutritional deficiencies, the guidance of a dietician is indispensable in preventing these deficiencies. Moreover, seeking advice from someone with expertise in the field of gluten-free substitute products, including options like amaranth, buckwheat, quinoa, sorghum, and teff, holds significant significance. These alternatives have the potential to enhance the intake of protein, iron, calcium, and dietary fiber for individuals with CD is advisable [3, 4].

The intake of products like amaranth alters the mechanism and inhibits the occurrence of the disease due to absence of gluten peptides (Figure 4). This causes inhibition of production of pro-inflammatory cytokines and in turn CD8+ intraepithelial cells preventing the onset of celiac related symptoms.

Gluten Free Products in Market

Over the past ten years, there has been a substantial increase in the production of gluten-free food products, largely because of more accurate diagnosis of CD and public debates about the potential health benefits of such foods. Projections indicate that this market is expected to experience significant growth, with a compound annual growth rate of 9.1% predicted from 2019 to 2025 [38]. The largest market for gluten-free products is North America representing roughly 59% of the total market. Growing attention has encouraged the launch of the one hundredth gluten-free food products in countries like US, Italy, UK, Spain, Germany, Australia, Brazil, Canada, and India [39].

Incorporating raw flours with high nutritional value is the most popular method of boosting the nutritional content of gluten-free breads. To produce gluten-free foods with high nutritional value, non-traditional flours are becoming more and more popular. These include pseudocereals (ama-

<table>
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<tr>
<th>Method</th>
<th>Subtypes</th>
<th>Explanation</th>
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<tr>
<td>Primary prevention</td>
<td>Infant feeding</td>
<td>Avoiding introducing gluten to infants who are genetically predisposed to developing CD could help prevent the disease. It was observed that introducing gluten between the ages of 4 and 6 months may reduce the chance of CD. In this specific timeframe, breastfeeding offers a safeguarding influence.</td>
<td>[3, 4]</td>
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<td></td>
<td>Antibiotics</td>
<td>A study indicates that experiencing multiple episodes of infections during early life can elevate the likelihood of developing CD later.</td>
<td>[36]</td>
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<td></td>
<td>Microbiota</td>
<td>There is substantial evidence of alterations in the microbiota being linked to certain autoimmune diseases. Research indicated that the microbiota in the duodenum and feces of individuals with CD is disrupted. This disruption is characterized by a reduction in the population of anti-inflammatory bacteria, such as Bifidobacterium species, and an increase in the population of Bacteroides species.</td>
<td>[4, 37]</td>
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<td>Secondary prevention</td>
<td>Case finding</td>
<td>Active case finding involves conducting thorough diagnostic tests on individuals displaying symptoms associated with CD. Screening for CD can involve the measurement of specific serum antibodies related to CD, such as tissue transglutaminase type 2, anti-endomysium, or deaminated gliadin peptides.</td>
<td>[3, 4]</td>
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<td>Mass screening</td>
<td>It has the potential to identify all instances of CD, including even those individuals who show no symptoms. Such screening allows for early detection and treatment, thereby reducing the negative health impacts and potential fatalities associated with untreated CD.</td>
<td>[3, 4]</td>
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<td>Tertiary prevention</td>
<td>GFD</td>
<td>It involves improving adherence to the GFD. The threshold for gluten capable of triggering an immune response has been estimated to be greater than 20 mg/kg. Sticking to GFD can be complex and challenging therefore individuals diagnosed with CD should consult the dietitians.</td>
<td>[3, 4]</td>
</tr>
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Amaranth, quinoa, and buckwheat), root and tuber flours (potato, cassava, sweet potato, and edible aroids: taro and yams), and leguminous flours (chickpea, lentil, dry beans, peas, and soybean) [39]. Amaranth has recently gained popularity in the development of gluten-free foods and diets majorly because of the presence of lipids, proteins, carbohydrates, dietary fiber and other constituents, such as squalene, tocopherols, phenolic compounds, phytates, and vitamins [39]. Rai et al. [40] reported that substituting corn starch with amaranthus flour had led to a remarkable 32% increase in protein and a substantial 152% boost in fiber content in gluten-free bread, all while maintaining sensory quality. Additionally, incorporating both quinoa and amaranth into a higher moisture dough (up to 65%) resulted in notable improvements in bread quality, including increased loaf volume and enhanced crumb softness. Amaranth storage protein has exhibited no immune toxicity in individuals with CD and has encouraged researchers to enhance the structural characteristics of quinoa and amaranth for use as alternative ingredients in the production of bread, pasta, and crackers. Bread that contains amaranth, quinoa, and sweeteners demonstrated comparable specific volume, firmness, and water activity compared to conventional bread, while boasting higher levels of protein, lipids, and ash.

In the study done by Bhatt et al. [41] to increase the nutritional attributes of gluten free muffins and its premix, black rice flour was taken as control (100%) and amaranth flour was incorporated at various levels (10%, 20%, 30%, 40% and 50%) with black rice flour. The findings showed that muffins and their premixes containing a 50% substitution of amaranth and black rice flour showed significant levels of total phenolics, flavonoid content, and antioxidant activities. Increasing substitution with amaranth flour significantly decreased muffins hardness and chewiness. And the least amount of hardness was obtained in 50% substituted formulation. The scanning electron microscope investigation showed that adding more amaranth four to muffins changed their microstructure because of starch and protein interactions. Texture, color, and sensory evaluations determined muffins’ total acceptability and when it was compared to other formulations, 50% substituted muffins had the highest level of acceptance. Piga et al. [42] studied the technological, nutritional, and sensory properties of gluten-free flatbread enriched with amaranth flour. For the making of the flat breads two different formulations that is rice flour, corn starch and rice flour, tapioca starch were taken in 50:50 ratio along with amaranth flour.

The findings showed that addition of amaranth flour when tapioca starch was used had adverse effects on the viscometric characteristics of the dough on the other hand it improved the texture of the dough. Flatbreads that were enriched with amaranth had improved color and a significant rise in polyphenol fractions but with less antioxidant activity. Over a three-day storage period, negative impacts were observed on starch retrogradation, toughness, and extensibility, particularly in the case of tapioca starch. Check-all-that-apply sensory testing revealed that incorporating amaranth flour led to increased perception of yeast odor and yeast flavor while reducing the softness, specifically in tapioca-based samples. A more favorable balance between technological, nutritional, and sensory attributes was achieved when amaranth flour was incorporated into the basic rice and corn formulation.

Advantages and Limitations of Amaranth Over Conventional Gluten Free Products

Advantages

Bakery products such as breads and cookies when made with raw and popped amaranth flour have uniform crumb texture, higher specific volume, high spread ability factor, hardness, reduced bake loss, enlarged diameter, and soft texture [43]. Amaranth proteins tend to increase water absorption and water solubility of solids when employed in extruded products because of their higher protein content and expansion rate was proved by Woomer and Adedeji [44].

Amaranth popping is high in selenium therefore gluten-free flours made from amaranth and oats can have amounts of selenium that are 2 to 9 times greater than flours manufactured from the more widely used grains such as corn, rice, and buckwheat [45].

Limitations

Addition of amaranth flour had adverse effects on the viscometric characteristics of the dough, particularly when tapioca starch was used. Over a three–day storage period, negative impacts were observed on starch retrogradation, toughness, and extensibility due to increased interactions between the amylpectin of amaranth and the amylose leached from tapioca starch. This led to synergistic impact on the viscosity and starch retrogradation [42].

Among non-grass alternatives, amaranth proved to be the least suitable for making pasta due to its negative effects on texture firmness, as well as its reduction in both cooking time and cooking tolerance [46].

Conclusion

Amaranth shows great promise as a dietary choice for those with CD because it not only provides a gluten-free alternative but also offers several possible health advantages. For people with CD, amaranth has become a great alternative to wheat and other grains because of its naturally gluten-free makeup. It has an outstanding nutritional profile, being high in protein,
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fiber, vitamins (including folate and vitamin C), and minerals (especially calcium, magnesium, and iron). Amaranth is also a good source of antioxidants, which might lessen the oxidative stress frequently experienced by people with CD. Its capacity to control blood sugar, lower blood pressure, lower cholesterol, inhibit harmful microorganisms, and offer strong antioxidant protection are just a few of its numerous health benefits. Its presence in a well-balanced diet can greatly improve general health and wellbeing. Amaranth has potential for the future as a treatment for CD. Furthermore, as celiac illness and gluten intolerance become more widely known, there will certainly be a rise in the demand for amaranth-based gluten-free foods.

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Conflict of Interest
None.

References


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