Review Paper

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Immunology

HUMAN MICROBIOME REPLENISHMENT USING PROBIOTICS: A TREATMENT FOR CELIAC DISEASE

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ABSTRACT Celiac disease (CD) also called gluten-specific enteropathy, affects about 1% of the worldwide population with significant clinical symptoms like malabsorption, fatigue, and duodenal mucosal damage which may lead to several other complications if not treated in early stages. A gluten-free diet is not feasible for every individual suffering from CD. Therefore, a safe treatment that complements a gluten-free diet is essential. This review aims to provide potential therapeutic strategies using microorganisms as probiotics that can be used to treat individuals with CD. It includes studies that show gluten digesting microbes isolated from humans can become a potential source for curing CD.

KEYWORDS : Celiac Disease, Microorganisms, Autoimmune disorder, Probiotics, Gluten, Gluten degradation, Therapeutic application.

INTRODUCTION

Celiac disease is an autoimmune disorder originating from an aberrant adaptive immune response against gluten-containing grains (wheat, barley, and rye) in susceptible individuals [8]. In celiac subjects' oral ingestion of gluten peptides (33-mer peptide present in α-gliadins and a 26-mer peptide from γ-gliadins) that escape intestinal degradation that results in an enteropathy with an impairment of the mucosal surface and, consequently, abnormal absorption of nutrients. These peptides are antigenically presented on HLA-DQ2 or HLA-DQ8, preferentially after deamidation of certain glutamines by the celiac disease auto-antigen tissue transglutaminase (tTG), eliciting a destructive Th1 T cell response [72,73]. Abolishment of these and related peptides results in an improvement in CD patients.

A strict gluten-free diet is the therapy of choice. Eliminating gluten from the diet significantly improves clinical symptoms characteristic of CD related to malabsorption, fatigue, and possibly associated autoimmunity and largely restores the duodenal mucosal damage (villous atrophy, crypt hyperplasia, T cell infiltration). However, the strict elimination of gluten from the diet is difficult to maintain and poses a significant social and financial burden to the patient. Therefore, an additive non-dietary therapy that relieves patients from a highly restricted gluten-free diet is necessary [74,75].

Till now certain bacterial strains have been discovered that can degrade gluten by producing gluten-digesting enzymes, which has led to the potential to develop probiotics-containing gluten-digesting bacteria. It has increased interest in finding bacteria that might be used in therapeutic products or could be a source of genetic material that could be transplanted safely into organisms currently used in safe probiotics [1]. The therapy currently used for gluten intolerance involves the usage of bacterial enzymes for oral supplementation which results in the degradation of gluten proteins in food before they reach the small intestine [76]. Moreover, it has been reported that probiotics, especially those found in the gastrointestinal tract have many other health benefits for patients with other digestive diseases [77,78]. Gluten-degrading bacteria can be a potential and cheap source as a non-dietary therapy for curing celiac disease.

Celiac Disease(CD)

Celiac disease is an autoimmune disorder. It occurs in susceptible individuals due to an aberrant adaptive immune response against gluten. In 1888, CD was first described by Samuel Gee, but only in 1953 did gluten become clear in the origin of this pathology [61-63]. Ingestion of gluten in celiac subjects results in an enteropathy with mucosal surface impairment and, consequently, abnormal absorption of nutrients [64-67]. The development of celiac disease, in addition to the ingestion of gluten, requires genetic susceptibility. The disorder almost exclusively occurs in people with the human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8 haplotypes [68]. Likely, other genetic and/or environmental factors are also involved in the disease onset as only a fraction of HLA-DQ2-positive and/or HLA-DQ8-positive individuals consuming gluten develop the disorder. The small intestinal mucosa is primarily affected by CD and the ingestion of gluten by predisposed individuals results in the development of a mucosal immune response, including an increased intraepithelial lymphocyte (IEL) count, and such immune responses eventually lead to structural changes in the gut, characterized by crypt hyperplasia (elongation of the crypts) and villous atrophy (blunting or flattening of the villi) [69]. However, the clinical manifestations of CD are broad, and patients may experience various extraintestinal symptoms or even remain asymptomatic in addition to gastrointestinal problems [70,71].

History Of CD

Celiac disease has an ancient history dating back to the 1st and 2nd centuries AD. Samuel Gee in 1888 gave the first clear description and suggested that dietary treatment might be of benefit. Various diets were tried without clearly recognizing the toxic components, with some success in the early 20th century. Wim Dicke in 1950 in his doctoral thesis said that oats, wheat, and rye exclusion from the diet led to dramatic improvement. Gluten, a protein component was shown to be toxic. Measurement of stool fat revealed the clinical condition shown by Dicke's colleagues, Weijers, and Van de Kamer [17]. Stool fat measurement can also recognize the condition in adults. In 1954, Paulley demonstrated histological abnormalities of the lining of the small intestine and in 1955 Royer techniques of per-oral biopsy were described and Shiner in 1956 afforded reliable diagnosis [18]. Studies of HLA antigens confirmed the concurrence in monozygotic twins suggesting a genetic component. Additionally, non-genetic factors seem likely. Circulating antibodies provide non-invasive screening tests and suggest an immunological mechanism of damage. Ulceration of the small intestine, adenocarcinoma, and Lymphoma, and various immunological disorders are associated. In 1955, a relationship with dermatitis herpetiformis was suggested by Samman [19] and established by Shuster and Marks in 1965 and 1968 [20-21]. In 1968, the Celiac Society (now Celiac UK) was founded; similar societies now exist worldwide. An extremely valuable service is provided by these societies [10].

Mechanisms/pathophysiology

Gluten is a complex mixture of glutenin (divided into high-molecular-mass and low-molecular-mass glutenin) and gliadins (divided up into α-gliadins, γ-gliadins and ω-gliadins) (Fig 1). Gliadins and glutenins are particularly rich in proline and glutamine amino acids; the high proline content renders these proteins fairly resistant to proteolytic processing by gastric and pancreatic enzymes and mammalian small intestinal brush-border membrane enzymes [49,50]. As a result, various long gliadin peptides are generated in the gastrointestinal tract that can activate the harmful immune responses seen in patients with CD.

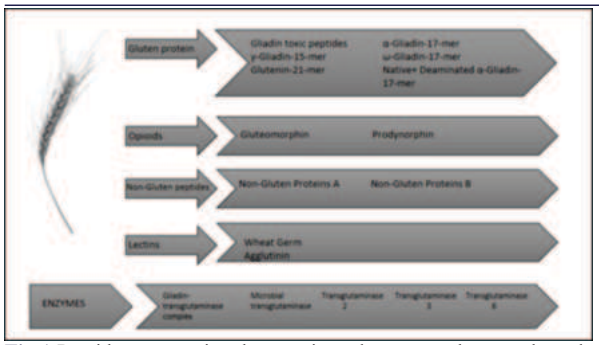

Fig 1 Peptides present in wheat grain and enzymes that can degrade them

Adaptive Immune Response

The adaptive immune response in CD is characterized by small intestinal mucosal gluten specific CD4+T cell responses [51,52] and antibodies towards wheat gliadin and the enzyme TG2 (transglutaminase 2) (encoded by TGM2). Native gluten peptides contain the amino acid glutamine at key positions, and TG2 can selectively deamidate these amino acids [53]. The biochemical modification causes glutamine residues to be replaced by glutamic acid, which increases the binding affinity of gluten peptides to HLA-DQ2 or HLA-DQ8 molecules on APCs [54] (Fig.2). The HLA-bound gliadin peptides are further presented to gluten-specific CD4+T helper cells [51,52]. Gluten-specific CD4+ T cells recognize the HLA-presented gliadin peptides by cell surface T cell receptors (TCRs). Interestingly, gluten-specific T cells carrying a TCR with different gliadin epitope recognition modes have been detected only in patients with CD [55]. As TCRs are generated in a random process, high-affinity TCRs specific for gliadin may be produced only in a minority of HLA DQ2-positive or HLA-DQ8-positive individuals, this explains why only a subset of these individuals develop CD [55]. Once activated, the gluten-specific CD4+T cells secrete various cytokines, including IFNγ and IL-21 [56], creating an inflammatory situation in the small intestinal lamina propria prone to tissue damage.

Innate Immune Response

In CD, innate immune responses are hallmarked by higher mucosal expression of IL-15, IL-18, and type I interferons, which are thought to be produced by stressed intestinal epithelial cells (IELs) and/or dendritic cells [57] (Fig.2). In CD, the number of IELs is increased and their amount correlates with the severity of mucosal atrophy. These cells display cytotoxic transformation, which is central to the induction of intestinal epithelial cell apoptosis driven by mechanisms involving Fas ligand [58], perforin, granzyme B [59], and type II integral membrane protein NKG2D [60]. These mechanisms contribute to the development of small intestinal mucosal villous atrophy.

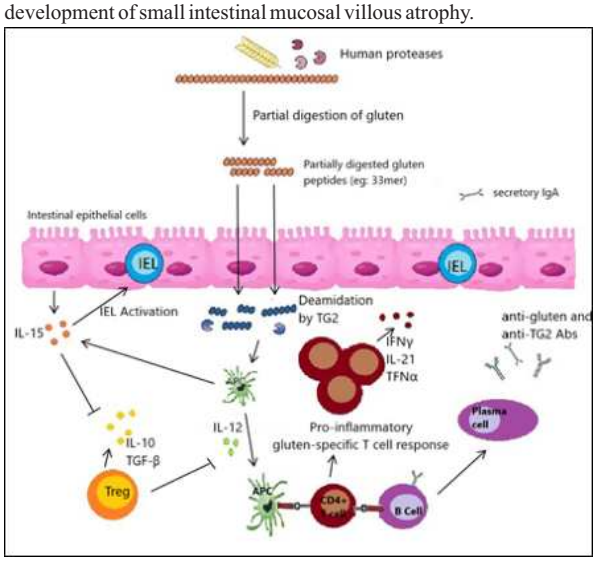

Fig 2 Mechanism of immune responses in Celiac disease

CD Diagnostic Criteria

Due to the variable clinical signs and symptoms, CD is heavily underdiagnosed. The basis for the diagnosis of CD is a combination of CD serology testing and the determination of small intestinal mucosal morphology. If CD is suspected, various serological tests, like TG2-Ab assays and EmAs (antibodies specific for TG2 in the endomysium, which is a form of perivascular connective tissue), can support the diagnostic procedure in selecting patients for endoscopy, upon which diagnostic duodenal biopsy samples are taken [9]. However, recently pediatric guidelines have incorporated a 'no-biopsy' arm in the diagnostic pathway thus, reducing the emphasis on duodenal biopsies [120].

Serological Tests

Anti-tissue transglutaminase antibodies: The best strategy for serological diagnosis is the blood detection of IgA anti-tissue transglutaminase antibodies (tTGA) by enzyme-linked immunosorbent assay (ELISA). tTGA shows a sensitivity around 97%, a specificity of up to 96%, and an accuracy of 98%. In tTGA positive cases, IgA anti-endomysial (IgA EMA) antibodies are employed as a confirmatory test due to their higher specificity (about 100% vs 91% of tTGA). “False nega¬tive” occurs in case of IgA deficiency. The IgA EMA represents the most specific test (approximately 100%), with a sensitivity of around 94% and a diagnostic accuracy of 97% [31]. However, EMA is routinely detected by indirect subjective immunofluorescence. These antibodies can also result falsely negative in case of IgA deficiency and children aged > 2 years [8].

Anti-gliadin antibodies: Except in younger children, the antigliadin (AGA) antibodies (IgG and IgA) are today no longer recommended because of their low sensitivity and specificity and inferior accuracy [32].

Deamidated gliadin peptides: Detection of antigliadin antibodies has been replaced by the recently developed immunoassays employing antibodies to deamidated gliadin peptides, IgA and IgG. To increase diagnostic accuracy, in the last years clinicians tend to prescribe serial testing.[8]

Histology

The gold standard to diagnose CD in adulthood is the intestinal biopsy sampled by endoscopy. Histology of celiac disease involves an integrated assessment of different entities: decreased enterocyte height, villous atrophy, crypt hyperplasia, and inflammatory infiltrates in small-bowel mucosal biopsies. The histopathology of CD based on one or more of these elementary lesions is subdivided into various diagnostic categories according to the Marsh classification [42]. Three conditions deserve specific mention as pointed out by Villanacci et al [42]: (1) “Autoimmune enteritis”; (2) Damage by drugs: especially non-steroidal anti-inflammatory drugs (NSAIDs) that cause morphological modifications likely to those of CD; and (3) The co-infection with Helicobacter pylori in the stomach.

Genetic Analyses

It is indicated only when a diagnosis is controversial. Large multicentre studies have shown that only 0.4% of celiac disease patients are both DQ2 and DQ8 negative [43]. It is consented to rule out predisposition to CD in family members of celiac patients in the absence of HLADQ2/8. HLA test helps detect potential celiac disease to suggest (if positive) or reject (if negative) the diagnosis. In patients with villous atrophy, HLA negativity, and negative serology should direct toward other possible causes of these histological alterations.

In vitro gluten challenge test

Gluten sensitive immunological activation in CD can be reproduced by in vitro gluten challenge test using culture cells from the duodenal mucosa [44].

Epidemiology Of CD

Before the 1990s, celiac disease was considered an uncommon disorder that mainly affected children and was limited to Western Europe. Improved diagnostics, including the implementation of CD-specific serological tests (transglutaminase 2 antibodies (TG2-Abs) and endomysial antibodies (EmAs)), have led to increased recognition of CD, in addition to making it possible to estimate the true prevalence of the disorder in the general population.[22-24] A 2021 systematic review of screening studies indicates that CD is now a major public health problem, as the pooled seroprevalence of Asia-Pacific region measured by TG2-Abs or EmAs in the general population can be as high as 1.2% (95% CI: 0.8–1.7%) [25]. Most screening studies have been performed in Europe, and the findings show variation between

different countries. High-prevalence countries in Europe include Sweden, Finland, Turkey, the United Kingdom, Italy, the Czech Republic and Portugal, whereas, in Russia, Estonia, Iceland, Poland and Switzerland, celiac disease is less common. The CD has been estimated to affect ~1% of the European population [26-28]. Similar studies performed in areas with high levels of European ancestry such as North America, South America and Oceania have yielded prevalence figures comparable to those in Europe. Population-based data on the prevalence of CD have also been reported from India and some countries in Middle Eastern Asia and Africa [29-30]. CD is now known to affect people worldwide. The disease is rare in some geographical areas such as Far East Asia and sub-Saharan Africa, although large epidemiological studies from these sites are still lacking. Epidemiological studies on CD prevalence in most populations are based on serological data, and invasive small intestinal mucosal biopsies have not established the diagnosis of celiac disease in all seropositive patients. Therefore, the Asia-Pacific pooled prevalence of biopsy-proven celiac disease, which is 0.61% (95% CI: 0.4–0.8%), is lower than the seroprevalence. The prevalence of CD is increasing over time based on of serological data. A recent meta-analysis also confirms a parallel increase in the prevalence of biopsy-proven CDs [25]. For each clinically diagnosed patient with CD, an average of five to ten seropositive individuals remains undiagnosed, usually because of atypical, minimal or even absent symptoms suggested by CD's seroprevalence figures [9].

5–8 million people are expected to have celiac disease in India, based on the three community-based studies by G. Makharia et al [45], Sood et al [46], and Lal et al [47].

Current Treatments For CD

Life-long gluten-free diet: The mainstay of treatment for CD remains lifelong strict adherence to a gluten-free diet. The gluten-free diet is used for a diet devoid of harmful gluten peptides, avoiding all food based on or containing wheat, rye, barley and all cross-breeds of these cereals. Primitive wheat varieties such as Kamut, einkorn and others may be less toxic for patients with CD, but this has not been convincingly shown in proper trials. Although a strict gluten-free diet is vital for patients with CD, studies suggest that the nutritional composition of such a diet might not be ideal. Gluten avoidance may lead to reduced consumption of beneficial whole grains (beneficial for cardiovascular health), which may increase cardiovascular risk [9].

Gluten-degrading enzymes: Enzyme supplement therapy with bacterial prolyl endopeptidases expressed by various microorganisms have been proposed to quicken gluten digestion in the gastrointestinal tract and thus destroy T cell epitopes [33]. An enzyme called AN-PEP degrades gluten peptides efficiently in a pH compatible with that found in the stomach. Therefore, this enzyme might be suitable for oral supplementation, but further studies are necessary [34].

Modified grains: Grains can be developed through selective breeding of early wheat species or small interfering RNA (siRNA) technology to mutate or silence immunostimulatory sequence [35].

Blocking gluten entry across the intestinal epithelium: AT-1001 is known to correct intestinal barrier defects. AT-1001 is currently the best-studied pharmacologic agent to treat patients with CD [36].

Rho/Rho kinase inhibition: It has been clarified that the increase in intestinal permeability is dependent on Rho kinase (ROCK) activity [37]. In addition to regulating tight junction structure and function, ROCK is known to regulate axon growth [38-39]. The drug could be used to establish whether ROCK inhibition can reverse the gluten-dependent increase in intestinal permeability in these patients [40].

Immunotherapy: Immunomodulators are developed for celiac disease resistant to dietary approach and especially for refractory celiac disease, including IL-15 blocking antibodies and human recombinant IL-10. Anti-IFN-γ antibodies and antibodies anti-TNF-α demonstrated a good tolerance among patients with inflammatory bowel disease, but their use in patients with CD needs more investigation. Another possible target of immunotherapy is represented by chemokines and their receptors, which play a significant role in the pathogenesis of CD. An alternative method studied for induction of tolerance to gluten is oral administration of a genetically modified Lactococcus lactis bacterium, capable of secreting deamidated DQ8-restricted gliadin epitope [8].

Vaccines: Clinical trials have been started with a prototypical vaccine based on a set of gluten peptides recognized by HLA-DQ2 in an immunodominant manner. A great interest is focused on vaccination, especially for raising the compliance of many patients which could beneficiate with a single-dose administration rather than a daily intake of other treatment options [41]. The risk of immune system activation related to the vaccine therapy and its side effects represent a still open question that need further investigations [8].

Microorganisms As A Treatment For CD

Several gluten-degrading enzymes from microbial sources have been discovered. Prolyl endopeptidases that target the conformationally constrained peptide bonds C-terminal to proline residues can be obtained from Sphingomonas capsulata, Flavobacterium meningosepticum, Myxococcus Xanthus and Aspergillus niger, have been pursued as drug candidates for the enzymatic treatment of gluten in celiac disease [79,80]. Prolyl endopeptidases have been demonstrated to neutralize the immunotoxicity of a pre-digested gluten preparation in vitro, ex vivo, and in vivo [81-84]. While promising regarding gluten-degrading activities, the enzyme referred to above originates from species not naturally associated with the human body. In addition, the toxicity of F. meningosepticum and A. niger limits their usefulness as probiotic agents [5].

A biologically more favorable and likely source for gluten-degrading enzymes would be the microbiome colonizing the human gastrointestinal tract [5]. Many reports have demonstrated that GI may harbor many beneficial bacteria for patients [85]. Most GI-colonizing microorganisms live in symbiosis with the host [1]. Research has shown that gluten-degrading bacteria naturally reside in the oral cavity [86,87]. The discovery of oral microorganisms secreting enzymes with such activities is significant since the oral cavity represents the entrance to the digestive tract that all ingested food must pass so gluten is mixed with the oral microorganisms in human saliva. The finding of gluten-degrading oral microbes may serve as a novel source for therapeutic gluten-degrading enzymes [5] and the production of potential probiotics that can be beneficial in treating CD. It has been demonstrated that certain probiotics contain elements that digest or alter gluten. Ingestion of probiotics containing these bacteria reduces the damage caused by gluten-contaminated foods and may even accelerate mucosal healing after initiating a gluten-free diet [88].

Mode Of Action Of Probiotics In CD

Probiotics strengthen the intestinal epithelial barrier

Bacteria present in probiotics are beneficial in maintaining the intestinal epithelial barrier. A study proves that probiotics enhance the expression of genes that participate in tight junction signaling, possibly reinforcing intestinal barrier integrity [96]. When intestinal cells were incubated with lactic acid bacteria, it was observed that the phosphorylation of adherence junction proteins was enhanced, positively regulating epithelial barrier function. Several studies have also shown that probiotics mediate the restoration of impaired barrier function [97].

Probiotics and adhesion to the intestinal mucosa

One of the main selection criteria for prospective probiotics is the ability to adhere to the intestinal mucosa as it prolongs their persistence in the intestine and thus allows the probiotics to exert their beneficial effects [98]. Several surface proteins of probiotic bacteria have been proven to promote mucous adhesion. To prevent pathogen binding, modifications in the intestinal mucins have also been done by probiotics. An anti-pathogenic effect on the host is conferred as the binding protein cleaves into an antimicrobial peptide that emphasizes the pleiotropic effect of probiotic surface proteins [99]. Moreover, gluten hydrolyzing probiotics showing adhesion properties also improve patients' overall health with CD [100].

Competitive exclusion of pathogens due to probiotics

Probiotic bacteria can inhibit pathogenic bacteria's attachment through steric hindrance at enterocyte pathogen receptors [99]. Probiotics also help eradicate Helicobacter pylori in the gut, decreasing the frequency of epigastric pain, vomiting, nausea, and diarrhea [101].

Probiotics produce antimicrobial compounds

Probiotic bacteria produce organic acids, mainly lactic and acetic acids, that exert potent inhibitory effects on Gram negative bacteria.[98] Bacteriocins are also produced by certain lactic acid bacteria, which encourages the establishment and increases the

prevalence of bacteriocin producing strains, thus directly inhibiting pathogens in the gastrointestinal tract [100].

Moreover, probiotics also produce anti-metabolic substances that inhibit the growth of fungi and other species of bacteria [102].

Probiotics showing immunomodulatory effects

Probiotics come in contact with intestinal epithelial cells, macrophages, lymphocytes, and dendritic cells [103]. Commensal and probiotic microorganisms interact with dendritic cells and initiate an appropriate response, such as the differentiation of Tho to Treg, which exhibits an inhibitory effect on the Th1, Th2, and Th17 inflammatory responses [104]. Due to the down-regulation of TLR expression by probiotics, intestinal inflammation is reduced. Probiotics secrete certain metabolites that prevent the entry of TNFα into blood mononuclear cells and arrest NFκB signaling in enterocytes [103].

DISCUSSION

Celiac is a rapidly increasing disease around the world. The characteristic feature of CD is the inflammation of the intestine resulting in the malabsorption of nutrients. CD occurs due to a combination of genetic and environmental factors.[89] A set of conditions can be associated with CD that includes "genetic disorders" such as Down syndrome, Turner syndrome, and Williams syndrome, and "autoimmune" or "neurological" disorders [8]. The individual suffering from CD not only have symptoms associated with the disease but also various other complications if not diagnosed in the early stage which includes (1) Osteoporosis (2) Enteropathy-associated intestinal T cells Lymphoma (3) Collagenous sprue (4) Refractory sprue (5) Ulcerative jejunoileitis [90] (6) Non-Hodgkin lymphoma (7) Small bowel adenocarcinoma [91] (8) Reproductive disorders [92].

Treatment and diagnosis of CD are very important at an earlier stage. The only fully beneficial treatment for this disease is to avoid gluten intake. Certain microorganisms that produce enzymes that can degrade gluten can become a potential source in treating patients with CD (Fig. 3). In past years, studies showing microorganisms' usefulness in treating CD patients have been very limited. The limitations are due to the small number of participants and the different methodologies used (Gliadin zymography, gluten hydrolysis, 16s ribosomal RNA sequencing, gelatin hydrolysis, PCR, and denaturing gradient gel electrophoresis). This results in a lack of standardization leading to dissimilar results [116].

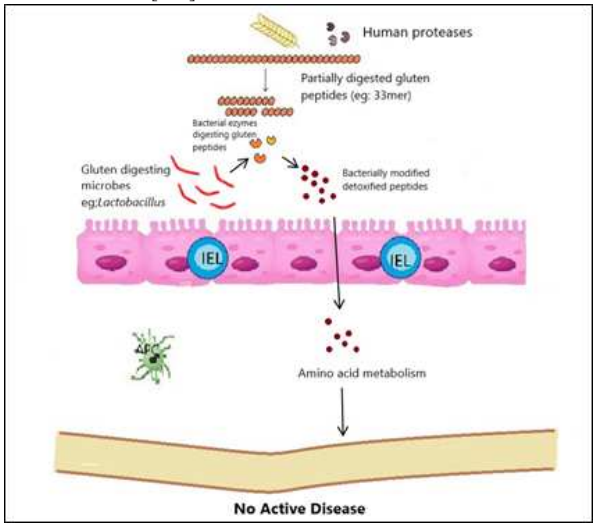

Fig. 3 Bacterial enzymes digest the toxic gluten peptides, which APCs can no longer recognize, producing no immune response, resulting in no active disease.

Recent research studies have shown that various sources can obtain gluten-degrading peptidases. Furthermore, these peptidases can be used for oral therapy for CD or to produce gluten-free foods from gluten-containing raw materials. Probiotics and oral enzyme therapy are believed to be promising candidates against gluten-free diets [117-119]. Therefore, from the above research papers reviewed, several bacterial strains that can be used for making probiotics including Bacillus licheniformis [16], Veillonella atypica, Streptococcus sps [13], Bacillus pumilus[12], Bacillus subtilis [15], Staphylococcus epidermis[14], Actinomyces odontolyticus, all Lactobacillus sps.[93-95] and Bifidobacterium sps.[88], Rothia sp. certain strains [11], Staphylococcus epidermis[14], and Actinomyces odontolyticus (Fig. 4). Several bacterial strains were found capable of gluten hydrolysis and can be effectively isolated from the source. These strains can be further categorized according to their nature as shown in the tables below and pie charts help to interpret the share of bacterial strains in each category easily.

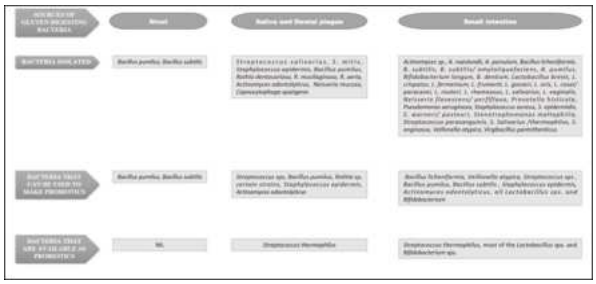

Fig. 4 Summary chart

Bacterial strains that can be used for making probiotics are *Bacillus licheniformis* [16], *Veillonella atypica, Streptococcus* sps[13], *Bacillus pumilus*[12], *Bacillus subtilis* [15], *Staphylococcus epidermis*[14], *Actinomyces odontolyticus,* all *Lactobacillus sps.*[93-95] and *Bifidobacterium sps.*[88], *Rothia sp.* certain strains [11], *Staphylococcus epidermis*[14], and *Actinomyces odontolyticus.* (Fig. 4)

Number of bacterial strains were found to be capable of gluten hydrolysis and can be effectively isolated from the source. These strains can be further categorized according to their nature as shown in the tables below, and pie charts help to easily interpret the portion of bacterial strains in each category (Fig.5, 6, and 7).

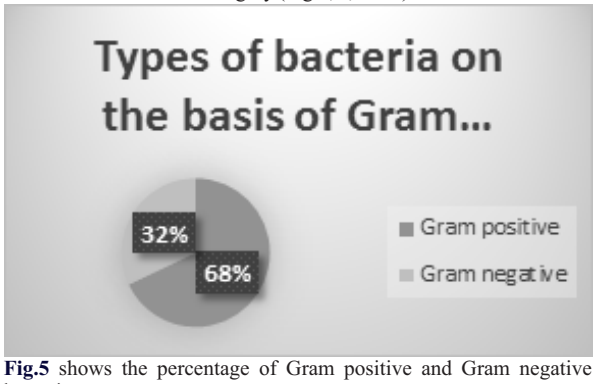

Fig.5 shows the percentage of Gram positive and Gram negative bacteria

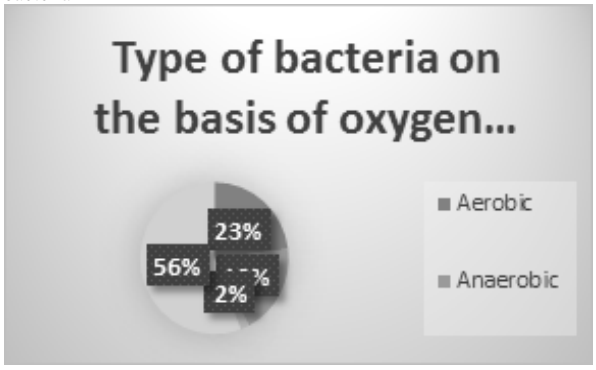

Fig.6 shows the percentage of aerobic, anaerobic, facultative aerobe, and facultative anaerobic bacteria.

Bacteria that can be used in therapeutics: The bacteria as a whole or its product can contribute to treating celiac disease. Pathogenic bacterial products such as gluten-degrading enzymes can be isolated and purified, which can be further given as oral supplements to individuals suffering from CD. Bacterial strains that are non-pathogenic can be used to make probiotics, which can be made easily available in the market and will be a cheap source to decrease the effects of gluten intake in CD individuals.

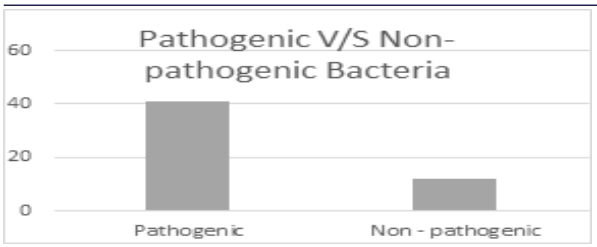

Fig.7 Compares Several Pathogenic And Non-pathogenic Bacteria.

The number of pathogenic strains is more than non-pathogenic strains (Bar chart 1), so oral enzyme supplementation can be one of the major methods for the treatment. Further studies must be conducted for purified enzyme isolation and its availability on a large scale.

Various probiotics are available commercially (table 1) that include non-pathogenic gluten-degrading bacterial strains which have many other benefits on human health.

Table 1 Showing Different Probiotic Products Having The Above-mentioned Gluten Degrading Bacteria Available In India.

Probiotic name	Bacterial strain
GNC Probiotic Complex with 25 Billion CFUs - 30 Vegetarian Capsules	*Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium animalis subsp. lactis*
WOW Life Science Probiotics Capsules	*Lactobacillus acidophilus, L. Plantarum, L. Fermentum, L. Casei, L. Rhamnosus, L. Reutri, L. salivarius, L. Paracasei, L. Gasseri, Streptococcus thermophilus, Bifidobacterium bifidum, Bifidobacterium lactis, B. Infantis, B. breve*
Yogut Capsule	*Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium infantis and Bifidobacterium longum*
California Gold Nutrition, LactoBif Probiotics, 5 Billion CFU, 10 Veggie Capsules	*Lactobacillus acidophilus, Bifidobacterium lactis, Lactobacillus rhamnosus, Lactobacillus plantarum, Bifidobacterium longum, Bifidobacterium breve, Lactobacillus casei, Lactobacillus salivarius*
Life Extension, Bifido GI Balance	*Bifidobacterium longum*
Hyperbiotics, PRO-Bifido, Probiotic Support for Ages 50+, 60 Time-Release Tablets	*B. infantis, B. bifidum, B. breve, B. lactis, B.longum, L.plantarum, L. acidophilus*
Probiotics 25 Billion Per Capsule, 14 Probiotic Strains	*Lactobacillus acidophilus, L. plantarum, L. fermentum, L. casei, L. rhamnosus, L. reutri, L. salivarius, L. paracasei, L. gasseri, Streptococcus thermophilus, Bifidobacterium bifidum, Bifidobacterium lactis, B. breve*
Jarrow Formulas, Bifidus Balance +FOS, 100 Veggie Caps	*B. breve, B. bifidum, B. longum , B. lactis*
Life Extension, Florassist Balance, 30 Liquid Vegetarian Capsules	*Lactobacillus acidophilus, Bifidobacterium lactis, L. paracasei, L. rhamnosus, B. bifidum, B. longum*
Boldfit Probiotics Supplement 30 Billion CFU for Men and Women	*Lactobacillus acidophilus, L. plantarum, L. Fermentum, L. casei, L. rhamnosus, L. reutri, L. salivarius, L. paracasei, L. gasseri Streptococcus thermophilus, Bifidobacterium bifidum, Bifidobacterium lactis, B. Infantis, B. breve*
INLIFE™ Prebiotics And Probiotics Supplement	*Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum*
Leeford Lee-Biotic Prebiotic And Probiotic Capsules	*Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium longum*
Nature's Way, Fortify, Daily Probiotic, Mood & Stress, 30 Delayed-Release Capsules	*Lactobacillus helveticus, Bifidobacterium lactis, Bifidobacterium longum*
Element Lifesciences Element's Probiotics 20 Billion CFUs 16 Probiotic Strains	*Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus brevis, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus gasseri, Lactobacillus reuteri, Lactobacillus salivarius, Bifidobacterium longum, Bifidobacterium infantis, Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium lactis*
Velgut Capsule	*Lactobacillus acidophils, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnasus, Bifidobacterium breve, Bifidobacterium longum*
Purayati Complete Probiotics	*Bifidobacterium bifidum , Bifidobacterium longum , Lactobacillus acidophilus, Lactobacillus rhamnosus*
Sporlac Plus Capsule	*Lactobacillus acidophilus, Lactobacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum*

CONCLUSIONS

Celiac disease is still a controversial and complex human disorder. There is a need for further research studies that prove that microbes can be used as treatment. Randomized clinical trials should be performed to introduce microbial products for the usual management of this disease in public. Several unanswered questions remain to clarify, including the real associations of CD with a decrease in natural gut microflora, especially microbes degrading gluten, and the working of these microbial enzymes to decrease the impact. There is still controversial opinion about the effective role of microbial products in celiac disease; what is to be elucidated is if it could offer permanent protection or if only temporary protection and delays the appearance of the disease. In addition, this could be a more defined and efficient way as the new therapeutic tools could improve quality of life by reducing complications and physical health or in terms of social life.

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