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Review Paper

The Potential of Algae in Treating Celiac Disease

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ABSTRACT

Compounds found in algae, such as bioactive substances, sulfated polysaccharides, and polyunsaturated fatty acids, have been found to have positive effects on the immune system. Previous research has shown that algae can also benefit digestive system disorders. They possess antioxidant and anti-inflammatory properties and can influence the balance of gut microbiota and maintain the integrity of the intestinal lining. Celiac disease (CD), a disorder caused by an abnormal immune response to gluten, results in inflammation and damage to the intestinal lining, leading to problems with nutrient absorption. Although a lifelong gluten-free diet is the only treatment option for this disease, it is challenging to adhere to. Therefore, recent studies have focused on finding supplementary or alternative therapies for celiac disease patients. Traditional medical treatments, like anti-inflammatory and biological drugs, are associated with significant side effects and are not suitable for supplementary therapy for this group of patients. Algae shows promise as a potential research area for treating CD; however, their specific effects on this condition have not been widely studied. The aim of this study was to gather current information and draw attention to the potential use of algae extracts in treating CD to encourage further research in this field.

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1. Introduction

Algae are a varied collection of water-dwelling organisms, encompassing both uncomplicated, one-celled organisms and intricate, multi-celled structures. They are capable of photosynthesis, containing pigments, like chlorophyll, while lacking the conventional features of roots, stems, and leaves found in vascular plants [1]. Algae can be found in a diverse range of environments, spanning from oceans, rivers, and lakes to ponds, brackish waters, and even snow, exhibiting a wide array of vibrant colors [2]. There are different classifications for algae depending on where they live. These include aquatic environments, like planktonic (floating), benthic (seafloor), marine, freshwater, lentic (standing water), and lotic (flowing water). Algae can also be found in terrestrial (land), aerial (in the air), subaerial (on the surface), lithophytic (on rocks), and various other habitats [3]. Compounds obtained from algae, such as bioactive substances with immunomodulatory properties, sulfated polysaccharides, and polyunsaturated fatty acids, have demonstrated beneficial effects on the immune system [4]. Algae contain a plethora of beneficial nutrients. These include proteins and amino acids, which are vital for tissue growth and repair in the body. Additionally, algae provide fatty acids, like omega-3 and omega-6, which play a crucial role in reducing inflammation. Furthermore, algae are a rich source of essential minerals, such as calcium, iron, magnesium, and potassium. They also contain an array of vitamins, including vitamin C, vitamin B12, and beta-carotene, which act as a precursor to vitamin A. Moreover, algae contain polyphenols and antioxidants that protect the body from damage caused by free radicals, as well as phenolic compounds exhibiting both antioxidant and anti-inflammatory properties [5]. Algae are an important reservoir of natural compounds that offer potential benefits in various areas, including cancer treatment, reduction of inflammation, and inhibition of acetylcholinesterase activity [3].

Previous studies have shown that algae have a positive impact on digestive system-related disorders [6]. For instance, algae polysaccharides can stimulate the growth of beneficial bacteria in the gut, which can help improve digestion, reduce inflammation, and improve gut microbiota [7]. Indirectly through the gut microbiota, algal proteins and carbohydrates that are not fully digested in the small intestine can enhance the immune response in humans [8]. Algae bioactive compounds, such as fucoidans and phenolic compounds with anti-inflammatory properties can help reduce inflammation in the gut [9]. It is worth noting that algal polysaccharides protect against inflammatory bowel disease (IBD) by specifically targeting inflammatory cytokines, adhesion molecules, intestinal epithelial cells, and intestinal microflora [10]. A study in humans demonstrated that green algae (*Chlorella reinhardtii*) can help improve human gastrointestinal problems related to constipation, diarrhea, and flatulence [6].

Celiac disease (CD) is a digestive system-related disorder that is caused by an abnormal immune response to gluten, a protein found in wheat, rye, and barley [11, 12]. These abnormal immune responses lead to an inflammatory response that damages the lining of the intestine and hinders nutrient absorption [12]. The prevalence of CD varies globally, affecting approximately 1% of the general population [12]. Individuals with untreated CD may experience a wide range of symptoms, including abdominal pain, diarrhea, weight loss, anemia, and fatigue [13]. This disorder is also associated with an increased risk of developing other autoimmune disorders, such as type 1 diabetes and thyroid disease [14]. The long-term implications of uncontrolled CD can include malnutrition, reduced bone density, infertility, and an increased risk of certain cancers [14, 15]. The only therapeutic option for this disorder is adherence to a lifelong gluten-free diet (GFD), which is difficult to maintain. Therefore, recent studies have focused on finding supplementary or alternative therapy for CD patients [11].

The therapeutic potential of algae in treating digestive system-related disorders is an area of active research. The current study aimed to attract the attention of researchers in treating CD using algae extracts by gathering current information in this regard (Figure 1). However, further studies are needed to fully understand the mechanisms of action and potential applications of algae in this context.

Materials and Methods

This study was performed by searching reputable scientific databases, such as ISI Web of Science, ScienceDirect, PubMed, and Scopus. For this purpose, all papers published in the period 2001–2022 were extracted by using keywords, such as algae in celiac, celiac novel treatment, algae therapeutic function, algae and oxidative stress, algae and inflammation, algae and gut microbiome, and algae and celiac pathogenesis. The included papers were the papers with available full texts, and written in English.

Results

The potential of algae in targeting different aspects of CD pathogenesis

Algae and intestinal epithelial integrity

CD occurs when the consumption of gluten compromises the integrity of the intestinal barrier, causing damage to the intestines [16]. This is primarily caused by gluten-derived peptides that are resistant to digestive enzymes, crossing the brush border and reaching the lamina propria [17, 18]. These peptides disassemble the epithelial tight junctions through the paracellular pathway, binding to the CXCR3 chemokine receptor on epithelial cells [19]. This leads to the release of zonulin protein, which disrupts the integrity of the tight junctions between epithelial cells [19]. Algae have shown potential in maintaining intestinal epithelial integrity, protecting the gut barrier, and improving gastrointestinal health [7]. The potential protective effects of extracts from Antarctic marine algae on damage to the intestinal epithelial barrier have been assessed. These extracts protect human intestinal cells from damage induced by lipopolysaccharide (LPS) and UVB [20].

The utilization of algal oil as a supplementary treatment shows promise in enhancing the concentration of certain tight junction proteins, thereby potentially promoting an effective solution [21]. Xu et al. [22] investigated the effects of algal oil containing docosahexaenoic acid (DHA) on colonic inflammation and intestinal microbiota in mice with induced colitis. The mice were treated with algal oil for two weeks after colitis induction. Algal oil supplementation improved colonic damage, reduced inflammation, and increased the expression of tight junction proteins. A team of researchers explored the potential anti-inflammatory effects of *Laminaria japonica* on intestinal inflammation. Their findings revealed that this seaweed enhanced intestinal barrier functionality and hindered the inhibition of proteins associated with tight junctions [23]. Feeding *Scytosiphon lomentaria* to mice with a deficiency in dietary fiber has been demonstrated to enhance the integrity of their epithelial cell layer by regulating specific proteins, like Claudine and Occludine [24]. Alginate oligosaccharides (AOS) are organic substances with natural bioactive qualities, boasting a wide range of beneficial attributes, such as anti-inflammatory, antioxidant, and prebiotic properties. These compounds are derived primarily from brown algae and can be created through either chemical or enzymatic breakdown of alginate [25]. In a mice model of dextran sodium sulfate (DSS)-induced colitis, the expression of Zonula occludens-1 and Occludin proteins was increased by an AOS-supplemented diet [26].

Algae and inhibiting oxidative stress

Some α-gliadin peptides of gluten protein, specifically P31–43, can enter cells. This occurs through a process called endocytic uptake. When peptide P31–43 accumulates in lysosomes, it activates certain signal transduction pathways and increases the levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are known as free radicals [27]. It has been suggested that oxidative stress is one of the mechanisms involved in gliadin toxicity. Various cell models have shown that exposure to gliadin leads to an imbalance in intracellular oxidation, resulting in higher levels of lipid peroxidation products, such as 4-hydroxy-2(E)-nonenal (4-HNE), an increase in the ratio of oxidized (GSSG) to reduced (GSH) glutathione, and a decrease in protein-bound sulfhydryl groups. The increase in oxidative damage caused by gliadin exposure can lead to changes in cell morphology, cell proliferation, apoptosis, and cell viability [27].

Algae employ two defensive strategies to protect cellular components from damage caused by ROS. The first strategy involves the use of antioxidant enzymes with high molecular weight, such as superoxide dismutase (SOD), glutathione reductase, catalase (CAT), and ascorbate peroxidase, or low molecular weight, such as ascorbate, flavonoids, carotenoids, glutathione, tocopherols, and phenols. These enzymes help neutralize the harmful effects of ROS generated through electron transport (O_2 •−, H_2O_2, HO•). The second mechanism involves repair enzymes that help fix and remove damaged macromolecules. While enzymatic antioxidants are crucial for detoxifying formed ROS, non-enzymatic antioxidants are more effective in preventing the production of ROS through excitation energy transfer [28]. Some algae, including macroalgae (seaweeds), are considered rich sources of natural antioxidants [29]. The antioxidant capacity of various marine algae, such as green, red, and brown algae species, has been extensively reported in the literature [29]. For instance, it has been noticed that microalgae generate a wide range of compounds, several of which possess antioxidant characteristics. These compounds include vitamins, such as A, C, and E, along with polyphenols, carotenoids, and bioflavonoids [30]. Surprisingly, the antioxidant power of microalgae equals or exceeds that of higher plants and fruits [31]. For numerous years, marine microalgae have consistently been viewed as a promising reservoir of high-value biomolecules, specifically antioxidant compounds [30]. Polysaccharides derived from brown algae may shield the intestine against harm caused by oxidative stress [7]. This protective effect might be achieved through a reduction in the production of ROS or by enhancing the

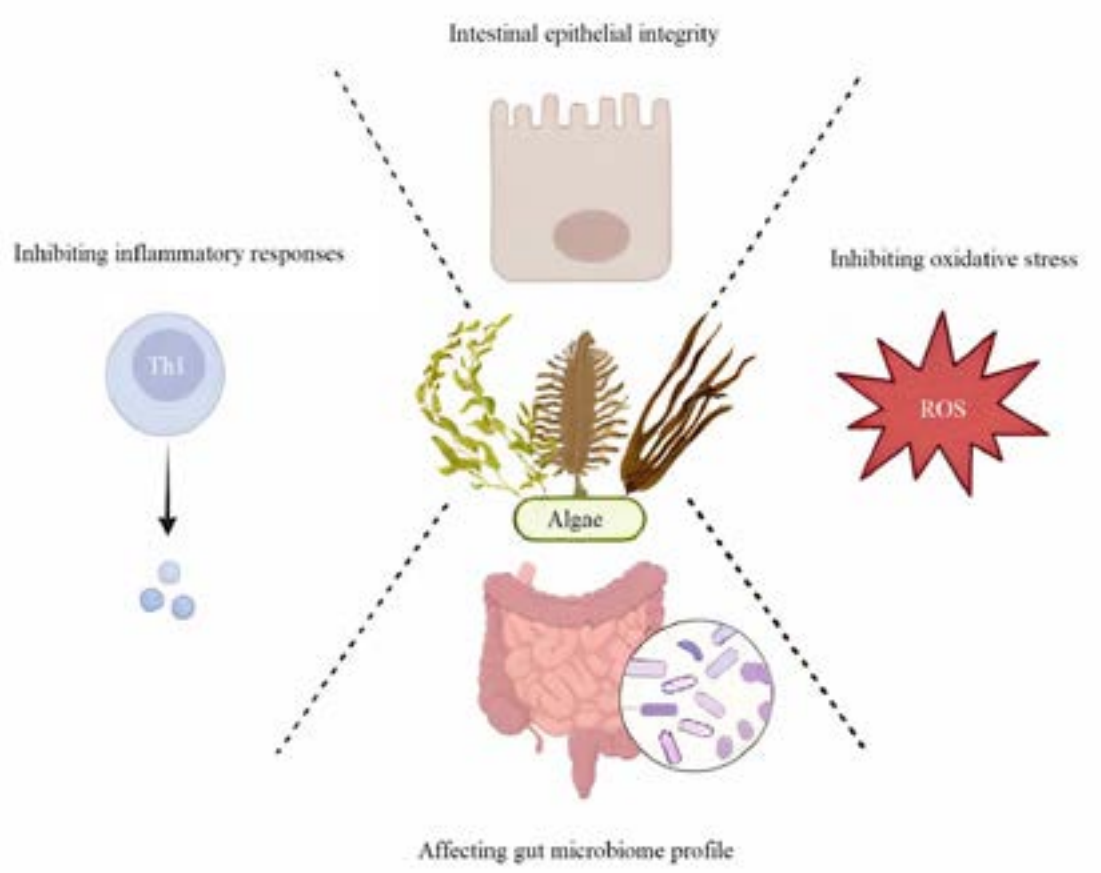

Figure 1. The positive impact of algae extracts on various aspects of celiac disease pathogenesis

functionality of antioxidant enzymes [32]. AOS reduces the production of nitric oxide and prostaglandin E2 and deactivates the nuclear-factor kappa B and mitogen-activated-protein-kinase signaling pathways in mice macrophage cell lines [33]. Additionally, it was found to enhance the activity of antioxidant enzymes, such as SOD and CAT in human umbilical vein endothelial cells [34].

Algae and inhibiting inflammatory responses

After the partially broken down, gluten peptides enter the lamina propria tissue, an enzyme called transglutaminase enzyme 2 (tTG2) modifies them and triggers the destructive immune response. The modified gluten peptides are then identified by antigen-presenting cells (APCs) that express HLA DQ2 and/or DQ8, such as dendritic cells (DCs). These APCs then present the modified gluten peptides to the gluten-specific CD4+T-cells and activate them. The gluten-reactive T cells undergo polarization along the T helper (Th) 1 pathway. As a result, they secrete proinflammatory cytokines, like interferon-gamma and tumor necrosis factor-alpha, resulting in increased gut permeability and enteropathy [13, 35]. Numerous experiments have shown that algal polysaccharides and algae extracts have the potential to treat and prevent gastrointestinal illnesses by serving as anti-inflammatory and gastroprotective agents [36-38]. These properties make algal polysaccharides particularly promising for treating intestinal inflammatory diseases. They are resistant to the effects of gastric juice and host enzymes, and there are various reports regarding their beneficial effects on reducing intestinal inflammation. Some of these positive effects are outlined below [39].

Potential therapeutic targets for chronic intestinal inflammation include selectins, integrins, and cadherin-like adhesion molecules, which play a crucial role in the migration of leukocytes in inflammatory regions [39]. Fucoidans, derived from brown algae, are polysaccharides that contain sulfated residues. The primary components of fucoidans are α-L-fucose and sulfate [40]. The potential therapeutic benefits of fucoidan are displayed through its ability to interact with selectins, effectively inhibiting inflammation in the early stages of its development [40]. Mice with colitis induced by DSS demonstrated a decrease in colonic mucosal injury and

crypt damage upon receiving fucoidan via intravenous administration [41]. It can also impede multiple enzymes and trigger apoptosis. One widely debated mechanism, by which fucoidan may exert its effects involves the reduction of mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) signaling pathways, leading to a subsequent decline in the synthesis of pro-inflammatory cytokines [42]. It should be noted that the biological activity of fucoidans can be influenced by differences in their chemical composition, particularly in relation to anti-inflammatory and immunomodulatory mechanisms [42]. For example, *Undaria pinnatifida* fucoidan has a ratio of fucose to galactose of 1.1:1.0, along with small amounts of uronic acids. This specific fucoidan has been found to increase IFN-γ levels, without causing significant changes in IL-4, IL-6, TNF-α, and NF-κB levels [43]. On the other hand, *Cladosiphon okamuranus* TOKIDA fucoidan has a higher content of uronic acid, with a ratio of fucose to glucuronic acid (GlcA) of 6:1. This variant has been shown to reduce IL-6 levels and attenuate the activation of the NF-κB signaling pathway [44]. Additionally, *Turbinaria decurrens* polysaccharide, with a ratio of fucose to galactose to xylose to mannose to rhamnose of approximately 6.0:1.3:1.1:1.0:0.6, has shown a reduction in the expression of COX-2, IL-1β, and the NF-κB signaling pathway genes [45]. Fucose and sulfate groups present in fucoidan can also affect its anti-inflammatory and immunomodulatory effects [42].

Sudirman and colleagues [46] examined the effectiveness of *Eucheuma cottonii* polysaccharides in reducing the inflammatory response in mice induced by DSS. The researchers administered the polysaccharides orally and observed improvements in weight loss and suppression in the expression of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-10. Zhu et al. [47] coated selenium nanoparticles with a polysaccharide derived from the green alga *Ulva lactuca*. This complex demonstrated potent anti-inflammatory properties and showed minimal toxicity. In an experiment involving mice with DSS-induced acute colitis, the administration of ULP-SeNPs significantly decreased the plasma levels of TNF-α, IL-6, COX-2, and iNOS in comparison to the control group. This beneficial effect was achieved by hindering the nuclear translocation of NF-κB, which is responsible for activating these pro-inflammatory cytokines. The diet supplemented with AOS improved the inflammatory responses in a mouse model of DSS-induced colitis by decreasing the levels of inflammatory markers, such as TNF-α and COX-2 [26].

Algae and their effects on gut microbiome profile

The microbiota plays a crucial role in determining human health. Imbalances in the microbiome, even in individuals without underlying health issues, have been associated with chronic medical conditions, including CD. Therefore, changes in the microbial profile are considered a potential trigger for the development of CD [48, 49]. Notably, many studies have observed variations in the levels of *Bifidobacterium* and *Lactobacillus* in the gut microbiota of individuals with CD. Moreover, patients with CD typically exhibit a higher abundance of Gram-negative bacteria, particularly *Proteobacteria* [48, 49]. Algal polysaccharides are believed to function as a fermentation substrate for beneficial gut bacteria, while also aiding in the regulation of the intestinal microbiota [39, 50]. Kong et al. [51] investigated the fermentation of sulfated polysaccharides from seaweeds *Enteromorpha prolifera* and *L. japonica* and their impact on human fecal microbiota. In vitro fermentation resulted in a decrease in pH and an increase in short-chain fatty acids (SCFAs), promoting a balanced gut microflora with higher levels of beneficial strains. This research suggests that sulfated polysaccharides from these seaweeds have prebiotic effects, and the molecular weight of the polysaccharides plays a role in their effectiveness. It has also been stated that AOS can enhance the population of bacteria responsible for generating SCFAs [52]. The native microorganisms found in microalgae serve as a crucial and initial defense mechanism against infections. Resident bacteria can prevent bacterial infections either by producing substances that have antimicrobial or antiviral properties or by outcompeting pathogens for resources and locations to attach, which is termed competitive exclusion [53-55]. As a result, studies have been conducted to explore ways of preventing infection by either consuming beneficial microorganisms (probiotic treatments) or consuming substances that stimulate the growth of helpful bacteria (prebiotic treatments). The prebiotic activity of several microalgae has been observed, with *Chlorella vulgaris* and *Arthrospira platensis* being examples that enhance the viability and survival of beneficial bacteria, like lactobacilli and bifidobacteria [56]. Additionally, co-culturing with *C. vulgaris* or *Nannochloropsis oculata* has been found to enhance the antimicrobial activity of *Sulfitobacter* spp. or *Roseobacter* sp., respectively, against *Vibrio anguillarum* [57, 58]. However, certain algae may have the opposite effect by sequestering vital nutrients and limiting their availability to bacteria [59].

Moreover, various algal cultures have been found to contain extracellular polymeric substances (EPS) that possess inhibitory properties against multiple bacterial and fungal isolates. These inhibitory properties were confirmed through agar diffusion and minimal inhibitory concentration (MIC) testing methods. Among the different EPS samples tested, the ones derived from *Gloeocapsa* sp. displayed the highest potency. Additionally, it was discovered that extracting compounds from *A. platensis* using different solvents resulted in methanolic extracts exhibiting the highest antimicrobial activity against bacterial pathogens [59].

Discussion

There are limited studies assessing the impact of incorporating algae on enhancing the quality of gluten-free products. For instance, Khemiri et al. assessed the impact of adding two species of green microalgae to gluten-free bread. According to their results, the addition of microalgae increased the protein, lipid, and ash content of the bread, and incorporating 3% microalgae led to a significant increase in iron and calcium levels. The fatty acid profile also changed, with an increase in linolenic acid and a decrease in the ω3/ω6 ratio. Additionally, the microalgae had a positive effect on the texture of the bread but did not significantly affect dough mixing properties. The color of the bread and its components also changed to more intense green-yellow tones due to the presence of pigments in the microalgae. Sensory analysis showed that the supplemented breads received higher scores in most parameters, with the 3% *Nannochloropsis gaditana* L2 bread being the most preferred overall. This study highlights the potential of using microalgae as a natural and sustainable ingredient to improve the nutritional and structural properties of gluten-free products [60]. Moreover, in another study, gluten-free noodles made from potato flour were fortified with 5%, 10%, and 15% spirulina algae to increase their nutritional value for individuals with celiac disease. The addition of spirulina algae increased protein, calcium, phosphorus, potassium, iron, and protein digestibility in the noodles. Sensory evaluation showed that the fortified noodles had better sensory characteristics compared to the control sample [61]. Nevertheless, additional comprehensive studies are required to assess the full potential of using algae as a supplementary treatment for individuals with CD. These studies have the potential to enhance the quality of life for patients and expedite the improvement of their overall health condition.

Conclusion

As a GFD may not fully control all CD-related manifestations, it is imperative to identify novel sources of medication in order to enhance the quality of life for CD patients. Due to their severe adverse effects, modern medical therapies, such as anti-inflammatory and biological drugs cannot be considered supplementary therapy for this group of patients. Algae holds potential as a subject for further research in this context; however, there is a notable dearth of studies examining their precise effects on CD.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. This study was approved by the Ethics Committee of the Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1402.283). This article has no human or animal sample.

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Authors' contributions

Conceptualization, data collection, investigation and writing original draft: Nastaran Asri, Mitra Rezaei and Reza M Robati; Review and editing: Mohammad Rostami-Nejad and Mona Zamanian Azodi; Supervision: Mohammad Rostami-Nejad.

Conflict of interest

The authors declared no conflict of interest.

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