





Gut Healing Natural Resource's Role in Management of Celiac Disease, a Brief Review

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Abstract

Celiac disease, also known as gluten intolerance, is an autoimmune digestive disorder in genetically susceptible individuals. Currently, a totally gluten free diet is considered as the only treatment for celiac disease, which means cutting out foods containing gluten protein from the diet completely. Strict adherence to this regimen can be challenging as several processed foods contain hidden gluten, added as flavor enhancer or texture modifier. In addition, the high cost and unavailability of gluten-free foods have led to patient's dissatisfaction. Moreover, there are celiac disease patients who have persistent symptoms despite dietary compliance. Emerging research have focused on discovering alternative non-dietary treatments for this disorder. There are herbal medicines and other natural resources with anti-inflammatory activity and valuable therapeutic effects in preventing or treating inflammatory diseases. As these are effective and affordable, several studies have focused on treating different diseases using these agents. However, there are few studies evaluating the effects and potential role of naturally derived compounds in celiac disease treatment. In this review, we gathered current information in this regard; hoping our article can serve as catalysts for researchers to pay more attention to natural therapies for celiac disease.

Keywords: carotenoids; celiac disease; dietary supplements; echinacea; polyphenols

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Introduction

Celiac disease (CD) is an autoimmune digestive disorder presents in genetically susceptible individuals (who express HLA class II haplotypes DQ2 and/or DQ8) [1]. Patients with celiac disease are intolerant of the gluten protein found in several naturally occurring grains

especially wheat, rye, and barley (oats contain a type of gluten that does not induce the immune responses in most CD patients) [2,3]. The worldwide CD incidence is estimated to be around 1%, which varies with age, gender, and in different geographic regions [4,5]. Due to the

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widespread use of sensitive and specific screening tests and also increasing knowledge of the general population and physicians about this disorder, it has been expected that CD prevalence will increase in the next few years [6]. The immune reaction that is triggered by gluten consumption leads to the intestinal inflammation and oxidative stress, increases intestinal permeability and prevents the digestive tract from nutrients absorption, which are crucial for optimal health [2,7]. There is variability in patients' response to gluten; CD can be accompanied by several intestinal and/or extra-intestinal presentations or it may even be without any clinical implications [8]. Currently, a totally gluten free diet (GFD) is known as the only treatment for CD, which means cutting out foods containing gluten protein from the diet completely [9]. Strict adherence to a GFD can be challenging as several processed foods contain hidden gluten, which is added as flavor enhancer or texture modifier [10]. Moreover, most of CD patients express dissatisfaction of the price and availability of gluten-free foods and believe that adherence to this regimen restricts their social activities such as having a meal in a restaurant and travelling. [6,11]. Furthermore, there are CD patients who continue to show persistent symptoms despite dietary compliance [12]. On the other hand, untreated CD can become life-threatening and increases the frequency of disease associated complications like osteoporosis and neurologic disorders, as well as severe complications like enteropathy-associated T-cell lymphoma (EATL) [13]. Thanks to better understanding of CD pathophysiology and molecular basis, emerging research have focused on discovering alternative non-dietary treatments for this disorder [14]. Many therapeutic strategies are being explored in this regard; however, none of them has been introduced as definitive alternative treatment for CD [15].

Herbal medicines and other natural resources have shown anti-inflammatory activity and valuable therapeutic effects in preventing or treating inflammatory diseases. As these are effective and affordable, several studies have focused on treating different diseases like inflammatory bowel disease (IBD), dermatitis, colitis, asthmatic and inflammatory lung diseases with herbal medicines [16-18]. Moreover, according to the results of studies, there are patients with medically diagnosed

gastrointestinal disorders who use complementary health care approaches such as herbal medicines in addition to conventional treatments to improve their health [19]. Patients choose these remedies because of their availability, low cost, and fewer side effects [20]. Nevertheless, the effects and potential role of natural compounds in celiac disease treatment have not been thoroughly investigated and remains neglected. In this review article, we have tried to gather current information in this regard, which can help researchers come up with new ideas for searching natural therapies for celiac disease.

Methods

In general, searches were developed in PubMed, Google scholar, and Scopus databases from September 1995 to June 2021. The following terms, alone or in combination, were searched: "medicinal plants", "herbal medicine", "plant compounds", "celiac disease", "treatment", "gluten intolerance", and "natural remedy". All in vivo, in vitro and clinical trials were considered.

Results and Discussion

To the best of our findings, limited studies have evaluated natural resources like plant compounds and plants, which have the ability to inhibit mucosal inflammation and oxidative stress, as a candidate therapy for patients with CD, that are presented in detail in the sections that follow.

Plant compounds and CD treatment

Polyphenols

Polyphenols are plant secondary metabolites with a strong potential in the enhancement of human health, produced by a wide variety of plants that are divided into main categories including phenolic acids, tannins, stilbenes, lignans and flavonoids [6]. It has been shown that polyphenols have antioxidant and anti-inflammatory activities through several mechanisms like reducing the concentration of arachidonic acid, prostaglandins, and leukotrienes by inhibiting phospholipase A₂, COX and LOX and suppressing iNOS induction and expression (Figure1) [21,22]. The results of studies on animals or cultured human cell lines showed the role of these ingredients in the prevention of cardiovascular diseases, cancers, diabetes, etc. [23]. Nevertheless, it has also been

reported that, polyphenols have an anti-nutritional effect in relation to protein metabolism by binding to them [24]. In fact, these metabolites can bind and sequester proteins especially proline-rich ones such as gluten and form hydrogen bonding and van der Waals interaction. Flavonoids, coumarins and tannins are known polyphenols with the ability to form insoluble complexes with gluten proteins [24]. Moreover, it has been found that, the concentration of polyphenols in the gastrointestinal tract reaches its highest values and it has attracted the attention of researchers to consider polyphenolic supplementation as a good complementary or alternative therapy for CD [6]. They suggested that polyphenols can interact with the cytotoxicity of gluten proteins through reducing their bioavailability, inhibiting digestive protease activity, transglutaminase 2 downregulation, regulating intestinal epithelial barrier function and immune responses. [6].

Carotenoids

Carotenoids are dietary fat-soluble components that belong to the tetraterpenes family and are absorbed by intestinal cells. Carotenoid's adoption has a role in controlling oxidative stress,

preserving intestinal barrier integrity, and modulating the predisposition to intestinal chronic inflammatory conditions and can be considered as an effective nutritional therapy for celiac disease. Carotenoids play their role through different ways including free radical scavenging activity (antioxidant function) and interactions with cellular signaling cascades, like nuclear factor κ B (NF- κ B) (Figure1) [21,25,26]. According to the results of epidemiological studies, carotenoids consumption is related to the reduced risk of cancer, cardiovascular diseases, osteoporosis, diabetes and inflammatory bowel diseases [27]. Although carotenoids intake is less than polyphenols, they reach higher plasma and tissue concentrations, and their plasma half-life is relatively longer than polyphenols [26].

However, it has been shown that, intestinal malabsorption syndromes such as CD are accompanied by lipid-soluble nutrients deficiencies. In this regard, Ward et al. evaluated serum and maculae concentrations of carotenoid in patients with malabsorption syndromes like celiac disease and reported lower macular carotenoid levels in such patients [28].

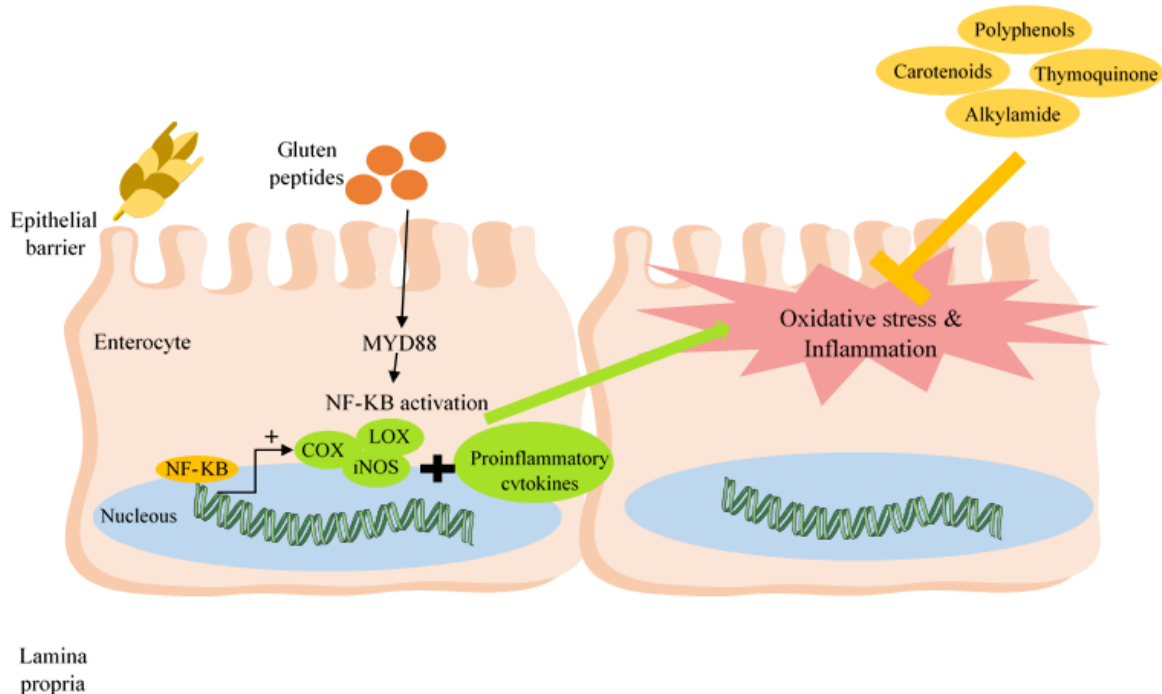


Figure 1. Polyphenols, carotenoids, thymoquinone and alkyl amides have the ability of inhibiting oxidative stress induced by gluten peptides in celiac disease. Gluten peptides induce MyD88-dependent NF- κ B activation in enterocytes. NF- κ B prompts COX, LOX, iNOS and proinflammatory cytokines transcription contributing to alteration in oxidative balance and inflammation process. MYD88: myeloid differentiation primary response 88; NF- κ B: nuclear factor kappa-light-chain-enhancer of activated B cells; COX: cyclooxygenase; LOX: lipoxygenase; iNOS: inducible nitric-oxide synthase

Worth of note is the results of Stefano et al. study on RAW 264.7 macrophages stimulated with IFN- γ gliadin to induce the inflammatory process. They found that lycopene (most abundant carotenoid in tomatoes) and quercetin (a flavonoid mostly found in onions, extra-virgin olive oil and broccoli), tyrosol (a polyphenol from white wine and extra-virgin olive oil) decreased iNOS and COX-2 gene expression at transcriptional level by preventing NF- κ B, interferon regulatory factor-1 (IRF-1) and signal transduction and activator of transcription -1 α (STAT-1 α) activation. They suggested that these compounds may have a role in controlling intestinal inflammation in celiac disease [29].

Curcumin is a xanthophyll carotenoid and low molecular-weight polyphenol that is known as the active ingredient of turmeric (*Curcuma longa* L.) with antioxidant, and anti-inflammatory ability. Curcumin was first identified in 1910 by Lampe and Milobedzka [30]. Different in vitro and in vivo studies revealed its potential therapeutic effect on various chronic diseases like IBD, pancreatitis, cancers and arthritis. [31-34]. By examining the 2000-years-old remains of teeth of a Roman young woman who had celiac disease (confirmed by CD responsible genes examining), researchers from the Tor Vergata University of Rome in 2020 found chemical traces of ginseng and turmeric in her dental plaque. They considered it as a sign of traditional Chinese medicine using in Greek and Roman medics for treating conditions like celiac disease [35]. Lopresti et al. [36] in their 8-week, double-blind study on 77 patients with digestive complaints in 2021 reported significant improvements in digestive problems and anxiety levels using curcumin extract, CurcugenTM. The patients well tolerated curcumin and showed no significant adverse events [36].

A combination of selected herbs and nutrients including curcumin, aloe, slippery elm, guar gum, pectin, peppermint oil, and glutamine forms the Nutrition Care (NC) Gut Relief Formula that support gastrointestinal health and improved GI symptoms in adults with digestive disorders [37].

Medicinal plants and CD treatment

Green tea

Green tea is produced from the leaves of the shrub *Camellia sinensis* L. and contains a wide array of organic compounds, like polyphenols [38]. Epigallocatechin-3-gallate (EGCG) is one of the main flavonoids in white and green tea,

that according to Dias et al. can interact with major CD immunodominant peptide (32-mer gliadin) and has an inflammation protective effect and wide range of health beneficial properties for CD patients [39]. Mota et al. [38] in their mice model study in 2015, reported analgesic and anti-inflammatory properties of green tea in chronic inflammatory disorders [38]. The preventive role of green tea in other chronic inflammatory conditions like metabolic syndrome and inflammatory bowel disease has also been reported in other studies [40-42]. Van Buiten et al. [42] in their in vitro study in 2018 showed that green tea polyphenol interacted with gliadin proteins and prevented their digestion by inhibiting digestive proteases. Using a transwell monolayer model they found that, the complex formed between these two components reduced gliadin abilities to stimulate intestinal permeability. Decreased secretion of proinflammatory cytokines by Caco-2 cells was also a sign of their ability of reducing inflammation. They suggested that green tea polyphenols have a protective effect against celiac disease. Moreover, it has been shown that, green tea catechins can prevent gliadin digestion in vitro that resulted in reduced gliadin-mediated intestinal permeability and inflammation [42,43].

Cocoa

Fresh cocoa beans in their natural state have high concentration of polyphenols including flavanols, mainly catechin, epicatechin, and procyanidins, which give them an extremely bitter flavor [44]. They also contain methylxanthines, namely theobromine and caffeine, protein, cellulose and mineral components. However, in a final processed cocoa product such as chocolate, the content of polyphenols significantly is decreased as a result of manufacturing processes. Since the seventeenth century, various studies considered cocoa and chocolate as potential medicines to treat wide variety of ailments including cardiovascular diseases [45]. Today, the antioxidant, antiradical and anticarcinogenic properties of polyphenolic constituents of cocoa and their immune response modulating ability have been considered in many scientific research studies [44,46-48]. Kramer et al. [47] in 2019 by examining CD inflammatory biomarkers like TG2, COX-2 and IL-15, showed that a cocoa extract enriched for procyanidin B2 applied to Caco-2 cells model of in vitro celiac disease

intervened in the inflammatory responses induced by IFN- γ - or gluten peptide p31–43.

Black seed

Black seed (*Nigella sativa* L.) which belongs to the Ranunculaceae family, is used for medicinal purpose to treat many kinds of illnesses. In fact, the most properties of this herb are attributed to thymoquinone, which is one of its many active constituents [49]. The anti-inflammatory, antidiabetic, antipyretic, antimicrobial, antitumour, gastroprotective, anti-*Helicobacter pylori* activity and immunomodulatory activities along with a very low degree of toxicity of black seed extracts have been demonstrated in lots of clinical and experimental studies [50]. Its gastroprotective effect is through inhibition of neutrophil infiltration and acid secretion from the parietal cells (by normalization of proton pump activity) [51]. Black seed can also increase nitric oxide production and mucin secretion and scavenge free radicals as an antioxidant (Figure1) [51,52]. It has also been reported that black seed can be used in skin conditions as eczema [53]. Osman et al. conducted a study with the aim of assessing the validity of black seed oil in treatment of refractory celiac disease (RCD) patients, who are resistant or unresponsive to a strict gluten-free diet and show malabsorptive symptoms and villous atrophy despite at least 6-12 months of dieting. They found that administration of black seed oil with GFD has immunomodulatory effects on refractory CD (better than GFD alone) and leads to complete histological recovery and significant decrease of serological markers. They suggested that black seed oil along with GFD can be applied for clinical management of refractory CD patients [54]. Osman and co-workers in another study found that treatment of adults with iron deficiency anemia caused by refractory CD, with black seed oil in addition to GFD for a period of 12 months was more effective than GFD alone in hematological, immunological and histology improvement [49,55]. He and his colleagues in a separate study on dermatitis herpetiformis, as an autoimmune skin disorder caused by CD which is treated by lifelong strict GFD adherence, found that adding black seed oil capsules to GFD for a period of 6 months enhanced the efficacy of the diet in the treatment of the disease leading to complete clinical, duodenal and skin histology remission and the absence of serological antibodies [49,56].

Echinacea

Echinacea is a member of the Asteraceae family and is a genus with important immunostimulatory and anti-inflammatory properties [57]. Echinacea plants contain different bioactive compounds including polysaccharides, caffeic acid derivatives, and alkyl amides [58]. It has been reported that its alkyl amides compounds have the ability of inhibiting cyclooxygenase and lipoxygenase enzyme activities (Figure1). The three most commonly used species for medicinal preparations are *E. angustifolia* DC., *E. pallida* Nutt., and *E. purpurea* L. Echinacea is known as potential treatment for recurrent aphthous stomatitis, which is one of the clinical manifestations of CD [59].

Robert's Formula, Bastyr Formula, is known as an old naturopathic formula which contains different anti-inflammatory herbs including *Echinacea spp.*, *Althea officinalis*, *Ulmus fulva* that have been reported to be effective in healing the digestive tract disorders and soothing the mucosal lining of the intestinal tract. Although it is widely used by natural medicine physicians, no formal research has been done to document the efficacy of the formula [60].

In a study on a 16-year-old-boy, with a previous diagnosis of CD, dermatitis herpetiformis, who was nonresponsive to 10 months strict GFD adherence, prescribing biocidin as an herbal formula containing *Echinacea purpurea*, *Echinacea angustifolia*, goldenseal, shiitake extract, white willow bark, garlic and grape seed extract showed beneficial effects in improving the patient's condition [61]. Nevertheless, it has also been reported that Echinacea supplementation has the ability of changing the GI microbiota. Especially it can increase Bacteroides group. According to the result of the study of Sánchez et al. which points to the role of *Bacteroides fragilis* in the pathogenesis of CD, this can be detrimental for CD patients [62,63].

Other medicinal plants

According to previous studies, other medicinal plants such as, cinnamon, cayenne pepper and cloves can also play roles in controlling the inflammatory conditions [57,64,65]; there are various medicinal plants such as *Coriandrum sativum* L., *Foeniculum vulgare* Mill, *Zingiber officinale* Roscoe, *Pinus roxburghii* Sarg and *Plumbago zeylanica* L., which are effective in

lowering the signs and symptoms of GI disorders [66]. Based on the different randomized controlled trials, certain herbal medicines like *Potentilla erecta* L., carob bean juice, apple pectin and peppermint oil have the potential to be used for different functional gastrointestinal disorders like IBS [67]. In this regard, Bahmani et al. in their ethno-pharmacological study published specifications of medicinal plants (including *Agrimonia eupatoria* L., *Amygdalus communis* L., *Anthemis tinctoria* L., *Bryonia dioica* Jacq., *Cuminum cyminum* J. F.Gmel., *Ficus carica* L. and *Galium verum* L.) from the Urmia region of Iran on different gastrointestinal tract disorders like diarrhea, constipation, bloating, etc. [68]. Gan et al. [19] in their systematic review in 2018 evaluated the prevalence of complementary medicine use by American and Australian gastrointestinal disorders patients (GI disorders are common in these two countries) including CD, IBD, IBS, liver disease, pancreatic disease, and intestinal disease patients. The result of their study showed a significant higher use of complementary medicines by these patients especially women who had higher education levels and income. Herbal supplements like turmeric, ginger, garlic, aloe, slippery elm, senna and fennel seed were among the most consumed products that were used by this group of patients [19].

Discussion

Several types of natural medications and naturally derived compounds are known to have inflammation controlling ability. Although these remedies are not devoid of risk, patients consider them to be safer than synthetic drugs and highly use them [19,20]. In a questionnaire-based study conducted by Nazareth et al. among CD patients in the United States, it has been reported that, of 423 patients, 100 (23.6%), especially who had symptoms at diagnosis, used dietary supplements like probiotics, fish oil, peppermint and turmeric to control CD symptoms and 336 (79.4%) of patients agreed with the medical professionals' support for complementary and alternative medicine. Supplement users reported improved quality of life but had persistent symptoms [69]. Moreover, in a cross-sectional study conducted by Bükülmez et al. in Turkey, it was reported that parents of children with celiac disease used garlic, kefir, oranges/kiwi fruit, spinach, oily fish, broccoli, pickles, potatoes, and bitter chocolate for enhancing the immune system during the COVID-19 pandemic period [70].

Our study gathered the results of in vitro, in vivo, and clinical studies that examined natural remedies for the treatment of CD and their effects are summarized in Table 1. There is still a need for further controlled clinical trials assessing the advantages and disadvantages of these alternative therapies for celiac disease together with enhanced legislation to maximize their quality and safety.

Table 1. Summary of mechanism of action of selected natural medicines in celiac disease

Medicinal plants/plant compounds	Main Structure	Mechanism of action
Green tea	Polyphenol	Antioxidant [21,22] Anti-inflammatory [21,22]
Cocoa	Polyphenol	Binding and sequestering proline-rich proteins [24] Reducing gliadin ability to stimulate intestinal permeability [24] Controlling oxidative stress (free radical scavenger activity)
Curcumin	Carotenoid	Preserving intestinal barrier integrity Modulating the predisposition to intestinal chronic inflammatory conditions Interactions with cellular signaling cascades, like $\text{NF-}\kappa\text{B}$ [21,25,26]
Black seed	Thymoquinone (monoterpene)	Anti-inflammatory Antipyretic Antimicrobial Antitumour Gastroprotective (through inhibition of neutrophil infiltration and acid secretion from the parietal cells) [50] Anti <i>H. pylori</i> Antioxidant (scavenging free radicals) Immunomodulatory Increasing nitric oxide production and mucin secretion [51,52]
Echinacea	Alkyl amide	Immunostimulatory Anti-inflammatory Inhibiting cyclooxygenase and lipoxygenase enzyme activities [57-59].

*: nuclear factor κB

Conclusion

Currently, a totally gluten free diet (GFD) is known as the only treatment for CD. Adherence to this regimen is highly restrictive and has several difficulties for patients. One reason is that gluten is present in just about everything we eat and drink. Various studies have focused on finding potentially useful medicinal herbs and other natural resources for therapeutic purposes, especially after increasing evidence of pharmaceutical drugs side-effects. In the present study, we pointed out natural remedies that may have the ability to be used in celiac disease treatment. In fact, our study gathered the available data about natural medicines with antioxidant, anti-inflammatory, antimicrobial, gastroprotective and immunomodulatory activities, which can be useful in controlling celiac disease gluten mediated inflammation. This wide range of natural elements and their low cost, availability, and fewer side effects compared to conventional methods have increased the willingness of patients to use them to improve their health. However, there is still no scientific basis for confirming that using one or more of mentioned natural medicines can be used instead of GFD for management of celiac disease.

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Author contributions

Mohammad Rostami-Nejad designed the study. Mostafa Rezaei-Tavirani, Nastaran Asri, and Somayeh Jahani-Sherafat, contributed to the concept of the review. Nastaran Asri performed the database and papers selection for the review and wrote the draft. Mohammad Rostami-Nejad, Somayeh Esmaeili, and Mahmood Khodadoost revised the manuscript. All authors approved the final version.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

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Abbreviations

CD: celiac disease; CM: complementary medicine; DH: dermatitis herpetiformis; EATL: enteropathy-associated T-cell lymphoma; EGCG: epigallocatechin-3-gallate; GFD: gluten free diet; GI: gastrointestinal; IBD: inflammatory bowel disease; IBS: inflammatory bowel syndrome; IRF-1: interferon regulatory factor-1; NC: nutrition care; NF- κ B: nuclear factor κ B; RCD: refractory celiac disease; STAT-1 α : signal transduction and activator of transcription -1 α