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REVIEW

Nightshade Vegetables: A Dietary Trigger for Worsening Inflammatory Bowel Disease and Irritable Bowel Syndrome?

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Abstract

The *Solanaceae* family of plants, commonly known as Nightshade vegetables or Nightshades, contains a diverse range of crops of over 2000 members with significant culinary, economic, and cultural importance. Familiar edible Nightshades include tomatoes, peppers, eggplants, and white potatoes. Many pharmacologically active compounds used in traditional medicine, including atropine and hyoscyamine, are derived from Nightshades. In addition to these beneficial pharmacologic agents, Nightshade-derived glycoalkaloid compounds, a key defense mechanism against predation, have been shown to disrupt intestinal epithelium and to potentially activate mast cells in the gut mucosa, leading to adverse symptoms in humans. There is a new appreciation that mast cell activation is an allergic inflammatory mechanism contributing both to pain in irritable bowel syndrome (IBS) and to gut inflammation in inflammatory bowel disease (IBD). Given their ubiquity in Western diets and their shared glycoalkaloid active compounds, edible Nightshades are attracting new interest as a potential trigger for worsening gut symptoms in functional and inflammatory gastrointestinal disorders. Here, we review the limited existing literature on the adverse effects of Nightshade consumption, including the effects of Nightshade-derived glycoalkaloids on IBD gut inflammation, and the under-recognized contribution of Nightshades to food allergies and allergic cross-reactivity. We then highlight new evidence on the contributions of mast cell activation to GI disorder pathogenesis, including potential linkages between Nightshade antigens, intestinal mast cells, and GI dysfunction in IBS and IBD.

Keywords Inflammatory bowel disease · Irritable bowel syndrome · Diet therapy · Mast cells · Food hypersensitivity · Solanum

Introduction

What Are Nightshades?

"Nightshade vegetables" belong to the *Solanaceae* family of herbs, shrubs, and trees. *Solanum* is the most representative and largest genus of the plant family *Solanaecae,* comprising over 2000 species distributed worldwide [1]. The most common crop plants in the Solanum genus include tomatoes, peppers, eggplants, potatoes, and tobacco plants (Fig. 1). Historically, Nightshades were used as mind-altering and hallucinogenic drugs in nearly every culture [2]. In medieval Europe, compounds found in Nightshade plants were used in anesthetics, and later in poisons [2]. Ladenburg and Schmidt recognized these alkaloid substances as the anticholinergic compounds atropine and hyoscyamine in the late nineteenth century [2].

Pharmacologically active compounds found in Nightshade plants include flavonoids, phenolic acids, alkaloids, and saponins, among others. In addition to beneficial pharmacological activities, widely used in traditional medicine [1], Nightshade plants may also trigger adverse reactions, including gastrointestinal side effects. Given the ubiquity of common Nightshade crop plants like tomatoes, potatoes, peppers, and eggplants in the Western diet and their shared, glycoalkaloid (GA) active compounds, there is a growing interest in this food group as a trigger for worsening gut

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Fig. 1 Common edible nightshade foods

health and disease. We review the limited existing literature on the adverse effects of Nightshade crop consumption, including the effects of Nightshade derived GA on IBD gut inflammation and food allergies to Nightshades. We also highlight recent evidence on the pathogenic contribution of mast cell activation in GI disorders, including the potential linkage between Nightshade antigens, intestinal mast cells, and GI dysfunction in IBS and IBD.

Popular Interest in Nightshades and Therapeutic Diets

Despite limited research regarding potential adverse effects of dietary Nightshade plants, there is significant interest in popular culture and social media. Celebrity endorsed diets that explicitly ban Nightshade plants [3] among other foods exert an unfortunate and unjustified influence on the general public's belief on diet and health. Other popular myths link consumption of Nightshades with worsening arthritis, osteoporosis, and migraines [3, 4].

There is mounting scientific evidence of the therapeutic value of diet modification in both IBD and IBS, (i.e., Mediterranean diet [5, 6] specific carbohydrate diet, low FODMAP diet) [7]. To date, there have been no dedicated studies in the role of Nightshade vegetable restriction in gastrointestinal diseases. However, there are examples of nightshade avoidance in certain exclusion diets being evaluated for therapeutic efficacy in IBD. For example, Nightshade vegetables are transiently reduced during induction in the Crohn's Disease Exclusion Diet (CDED) but are reintroduced during maintenance. The Auto-Immune Protocol diet recommends avoidance of Nightshade vegetables along with grains, legumes, dairy, eggs, coffee, alcohol, nuts and seeds, refined processed sugars, oils and food additives with personalized reintroduction [8]. While it is difficult to draw any conclusions regarding the impact of Nightshades on IBD symptoms from these studies alone, the notable exclusion of these foods is cause for further investigation.

Potato Glycoalkaloids (GAs) and IBD

The GAs are a class of nitrogen-containing steroidal glycosides commonly found in plants of the Solanum genus within the Nightshade family and its agriculturally significant crops: potato, tomato, pepper, and eggplant [9]. Historically, GAs have been associated with a plant's ability to resist pests and demonstrate concentration-dependent toxicity to many organisms, including insects and humans [10]. Solanine poisoning from green or sprouted potatoes have been reported as early as 1979 [11]. The reason green/sprouted potatoes are especially dangerous is because the highest concentration of these GAs resides in metabolically active areas such as the green skin, stems, sprouts, and can be increased by environmental factors such as exposure to bright light, immaturity, and storage in low temperatures [12].

Several potential mechanisms of solanine toxicity have been described which include inhibiting cholinesterase activity [13], disrupting active transport of sodium and calcium across cell membranes [14], and binding 3b-hydroxy sterols with subsequent disruption of sterol-containing membranes [15] such as those of the intestinal epithelia. Systemic toxic effects of GA poisoning include gastrointestinal injury with vomiting and diarrhea, tachycardia, hemolysis, headache, neurotoxicity, and death [12].

One of the most recognizable members of the Nightshade family is the modern potato (*Solanum tuberosum L.*), a crop grown in approximately 80% of all countries. Attention has been focused on the GA content of potatoes due to its potential toxicity and because GAs are present in all commercial potatoes [16]. 95% of the GA content in potatoes consists of a mixture of α-chaconine and α-solanine, concentrations which can be increased through physical processes such as aging, frying, high temperature storage, and exposure to light [17]. In an in vitro study using mouse small intestine epithelial cells, He et al. showed that Nightshade-derived α-chaconine disrupted the cell cycle, inhibited cellular proliferation, accelerated apoptosis, destroyed the mechanical barrier, and increased the permeability of the mucosal epithelium [18].

Despite the known toxicity of GA on the gastrointestinal tract and observations of higher incidences of IBD in high potato-consuming countries [19], there have been limited studies evaluating the potential effects of oral GA intake on IBD colitis. Patel et al. showed GAs such as solanine and chaconine can disrupt the intestinal barrier integrity in interleukin-10 (IL-10) knock-out mice, which are genetically predisposed to develop IBD compared to control animals. In vivo oral feeding experiments of the same GAs at physiologic concentrations demonstrated aggravation of histologic colonic injury in these murine models [20].

The potential for the potato and its method of preparation to contribute to gut inflammation, has prompted investigation on deep-fried potatoes, or french fries. French fry consumption has increased dramatically over the past 50 years in the U.S. and Western countries. This is consistent with the rising consumption of high fat, low fiber, and ultra-processed foods over the past five decades which parallels the epidemiological trend of rising IBD rates [21]. According to a cross-sectional, secondary analysis of the 2017–2018 National Health and Nutrition Examination Survey measuring the makeup of vegetables intake found that french fries and other potato dishes made up three of the five top contributors to discrete vegetable intake [22]. Compared to the general population, IBD patients have higher intake of french fries [23].

A potential mechanistic link between fried potato consumption and gut inflammation was explored by Lablokov and colleagues, who demonstrated that high GA containing deep-fried potato skins could aggravate intestinal inflammation in two murine models of IBD. IL-10 deficient mice and mice fed dextran-sodium-sulfate (DSS), a chemical known to induce murine colitis, were fed deep-fried potato skins with high GA content. Compared to animals fed control diets, the researchers found significantly elevated levels of ileal interferon gamma (IFN-γ) in the IL-10 deficient mice model and significantly elevated levels of proinflammatory cytokines IFN-γ, tumor necrosis factor alpha (TNF-α), and IL-17 in the colon of the DSS colitis mice who were fed a diet enriched with fried potatoes [24]. These results suggest that consumption of deep-fried potato products (with high GA content) could be a potential aggravating dietary factor for IBD exacerbation. However, it is important to note that French fries are also high in fat and high fat diets have been shown to alter gut microbiota and homeostasis [25]. These factors together could create a perfect storm for French fries to be a potent dietary aggravator of IBD.

Nightshade Food Allergy

A National Institute of Allergy and Infectious Disease (NIAID) expert panel defined food allergies as "adverse health arising from a specific immune response that occurs reproducibly on exposure to a given food" [26]. In both adult and pediatric populations, food allergies can cause significant morbidity and mortality through cutaneous, gastrointestinal, and respiratory symptoms. Although firm data on food allergy prevalence is lacking, there has been a rise in food allergy rates over the last 2–3 decades [27] which have disproportionately affected individuals in industrialized countries consuming a Western diet.

Though not as commonly seen, reported cases of allergic reactions to the major crop plants in the Solanum genus–eggplant, tomatoes, and potatoes–[28–31] have increased. One cross-sectional analysis of 741 subjects from Mysore City, Karnataka, India, estimated prevalence of IgE mediated eggplant allergy to be 0.8%, with higher rates of sensitization in females [32]. Multiple molecules can trigger allergic reactions to Solanum genus crops, including lipid transfer proteins (LTPs), profilin, and polyphenol oxidase (PPO), among others [33].

LTPs and profilins are widely cross-reactive plant-produced food allergens most frequently present in the surface of fruits such as apples, peaches, apricots, strawberries [34]. They are small and stable proteins resistant to heat and acidity, allowing them to exert effects after oral ingestion. Allergy to LTPs occurs from primary sensitization in the GI tract and results in LTP syndrome, which can lead to frequent systemic reactions including anaphylaxis [34]. LTPs are among the most common causes of food allergies in adults living in the Mediterranean Basin and the main cause of primary food allergy in Italian adults [35]. While profilins are less commonly associated with allergy than LTPs, they have become more studied in recent years due to the possibility of cross reactivity.

LTPs have been implicated in cases of eggplant and tomato allergy. In a comparative study by Asero et al. investigators evaluated 49 patients who were monosensitized to LTP for food sensitivities using skin prick test for a wide variety of vegetables. They found 4% with IgE reactivity to eggplant [36]. In another study, Gubesch et al. challenged 60 patients with pollen allergy to three previously un-experienced vegetables–including Ethiopian eggplant–in order to assess the allergenicity of common pan-allergens, including LTPs and profilins. First, both LTP and profilin were detected by animal antibodies in all vegetables. Then, IgE binding to LTP and profilin from subjects were proven by immunoblot analysis and enzyme-allergosorbent test [37]. Lastly, the clinical relevance of IgE binding to allergens was assessed by skin prick testing and oral food challenge. 10% of patients developed an oral allergy syndrome under oral food challenge of the Ethiopian eggplant despite having never had this food previously, suggesting previous sensitization to LTP was enough to elicit an allergic reaction [37]. In the same study, a second group of participants with specific food allergies were also evaluated for sensitivity to the same three novel foods. In a group of 10 adults with tomato allergies, most of them were IgE reactive to Ethiopian eggplant [37]. This is not surprising given that both foods are part of the Solanum family and tomato allergy has also been attributed to LTP reactivity [38]. These results suggest a potential cross reactive mechanism to LTPs within the Nightshade family.

Many of the allergens identified in plant foods are known to have essential physiologic roles in plant biology. This is also the case for the Nightshade family. A major allergen

identified in the potato is patatin (Sola t1), a 43 kDa protein, which has shown lipid acyl hydrolase and phospholipase activity [39]. Minor allergens of potatoes including Sola t2-Sola t4, proteins ranging between 16 and 21 kDa in size, are known to be trypsin inhibitors [40]. One major identified tomato allergen (Sola l 2) has B-fructofuranosidase activity while some of the minor antigens have been shown to possess polygalacturonase and pectinesterase activity involved in fruit ripening [41].

Similarly, many potential allergenic proteins have been identified in the eggplant ranging between 26 and 71 kDa [42]. While Babu and colleagues identified allergens in all parts of the eggplant, the highest concentration was localized in the peel [42]. In a follow-up study, this group demonstrated that some of the allergens identified in eggplant peel are polyphenol oxidases (PPOs), an important enzyme in eggplants [41]. The higher prevalence of allergens in the external peel is commonly seen across other allergenic edible fruits such as peaches and is likely an evolutionary defensive measure against external predators. It is not unexpected that the defensive proteins on the outer layer of the plant will differ from those within the pulp of the fruit and can explain the allergen concentration differential seen in the eggplant [42].

Cross Reactivity and the Latex-Fruit Syndrome

Based on the protein molecules implicated in allergy to Nightshade plants, cross reactivity can occur within and outside of the Solanum family. Becker and colleagues identified antigenic glycoprotein in tobacco, also a member of the Nightshade family, which was found to induce hypersensitivity reactions in 12 volunteers [43]. They found similar cross reactive antigens in other members of the Nightshade family including eggplant, potato, tomato, and green pepper [43]. The cross reactivity can occur outside of the Solanum family as well. In a study on the natural course of pediatric allergy to potato, De Swert and colleagues suggest allergy to cooked potato is a risk factor for the development of pollen allergy [44].

The Latex-Fruit syndrome describes an association where approximately 30–50% of individuals who are allergic to natural rubber latex show an associated hypersensitivity to plant foods such as the Nightshades tomato, potato, and bell pepper [45]. This is due to allergen cross reactivity from IgE antibodies that recognize structurally similar epitopes on different proteins including patatin like proteins and profilin [45]. Reche et al. showed cross-reactivity between tomato, potato, and latex allergy most likely through the major potato allergen patatin [46]. It is worth noting that there is likely an evolutionary role for these high conserved plant proteins in defense against predators such as insects, which can explain why these allergenic proteins are shared across so many different plant species and lead to cross reactive antibodies in allergies.

Mast Cells and the GI tract

Mast cells are immune cells of myeloid lineage and are major effectors in allergic reactions through degranulation and release of inflammatory, vasoactive, and nociceptive mediators. They are activated by a wide variety of stimuli. While the most well known mechanism of activation is cross linking of antigen-specific IgE antibodies, Mast cells can also be activated by toll-like receptors, G protein coupled receptors, complement peptides, and platelet activating factors [47]. Upon activation, mast cells can either release preformed molecules stored in granules including histamine, proteases, TNF-α, or through de novo synthesis of mediators including cytokines, chemokines, growth factors, and lipid mediators.

The intestinal epithelial barrier is an interface with the external environment and must simultaneously maintain immune tolerance to millions of microorganisms that live in the intestinal lumen, perform gastrointestinal nutritive functions, and also establish immune tolerance toward dietary antigens [48]. In the gut, mast cells located near mucosal surfaces, especially those proximal to blood vessels and nerve fibers, help the intestinal epithelium integrate external and internal signals, coordinating immune response and maintaining homeostasis.

Mast Cells and GI Disorders: IBD and IBS

Mast cells have been mechanistically implicated in several intestinal disorders, most notably IBD and functional GI disorders such as IBS. Several observational studies have suggested a role for mast cells in IBD pathogenesis and progression. Gelmann et al. observed accumulation of mast cells in hypertrophied and fibrotic muscularis propria in strictures of Crohn's disease (CD) patients [49], while Andoh et al. noted increased mast cells in the mucosa, submucosa, muscularis propria, and surrounding fat in active CD [50]. More recent studies have shown an increased number of mast cells in the colons of both CD and ulcerative colitis (UC) patients [51] as well as increased expression and release of mast cell mediators, suggestive of increased mast cell activation [52]. In pre-clinical models of IBD colitis, mast cells have been shown to be involved in both the acute and sustained inflammatory response [53]. Chen et al. found that inflamed UC regions were distinguished by Mas-Related-G-Protein-coupled Receptor X2 (MRGPRX2)-mediated activation of mast cells, but there was less activation in those who had a UC-protective genetic variant of MRGPRX2 [54]. These results suggest genetics can play a modulatory role in Mast

cell mediated colonic inflammation through an IgE independent mechanism. While these studies are supportive of a potential role of mast cells in IBD, future studies are needed to ascertain the effectiveness of using mast cell stabilizers/antagonists in symptom relief of IBD.

Similar to IBD, studies have shown increased mast cell infiltration and mediator release in colonic mucosa of IBS patients compared to controls [55]. A prevailing theory of IBS pathogenesis is that the classic symptoms of abdominal pain and altered bowel habits arise from a disruption of the gut-brain axis where intestinal nerves are hypersensitive to a variety of stimuli and normal functioning including gastrointestinal stretching and food motility feel more painful. The disruption of the gut-brain axis may be immune mediated. The existence of post-infection irritable bowel syndrome (PI-IBS), where an individual has new onset Rome-criteria positive IBS following an acute episode of gastroenteritis, suggests a role for the immune system in the pathogenesis of IBS [56]. While the pathophysiology of PI-IBS is not well understood, postulated mechanisms include increased density of T lymphocytes in the lamina propria, increased gut permeability, and altered serotonin metabolism as a sequelae of ramped up immune activity during acute infection [56].

A recent paper by Aguilera-Lizarraga et al. demonstrated that bacterial infection can trigger IgE antibodies to a dietary antigen, and upon subsequent oral ingestion of said antigen, a mast cell dependent mechanism induced visceral pain [57]. Furthermore, the authors injected food antigens (gluten, wheat, soy, and milk) into the rectal mucosa of 12 patients with IBS and observed local edema and mast cell activation [57]. These results are significant because it suggests a potential allergic mast cell mediated mechanism for the abdominal pain seen in IBS [58]. There have been several studies using mast cells as a therapeutic target in treating IBS symptoms as reviewed by Zhang et al. [59]. For example, Wouters et al. demonstrated that Ebastine, a histamine 1 antagonist, reduced visceral hypersensitivity, symptoms, and abdominal pain in patients with IBS [60]. In a separate placebo controlled trial, 8 weeks of treatment with Ketotifen in 60 IBS patients reduced IBS symptoms and improved quality of life [61]. While these studies are promising, they have major limitations including small sample sizes, selection bias, and poor design. In addition, the drugs used often work through multiple mechanisms of action, making it difficult to conclude that efficacy is from mast cell related mechanisms only.

Mechanisms of Nightshade Induced Mast Cell Activation in GI Dysfunction

There is evidence that Nightshade vegetables can directly activate mast cells in the gastrointestinal tract of humans (Fig. 2). Pramod et al. demonstrated potato lectin activating basophils in vitro and Mast cells in vivo, in atopic subjects through a non-allergic food hypersensitivity mechanism, defined as a "special type of non-immunological reaction, in which a substance in the food triggers the mast cells/basophils directly or with the involvement of non-specific IgE antibodies [62]". Lectins are reversible carbohydrate binding proteins found in all plants that can mediate non-allergic food hypersensitivity. Specifically, lectins can bind to N-linked glycoproteins on the heavy chains of IgE molecules. These newly lectin-bound, nonspecific, IgE molecules on mast cells and basophils subsequently cross link and degranulate, mimicking a similar end result to a true allergic reaction [62]. These authors further postulated that other similar food lectins, such as tomato lectin, may induce a similar reaction.

We propose two additional pathologic mechanisms based on existing studies on common Nightshade plant foods. Active compounds such as GAs seen in Nightshade plants like potatoes can have a direct toxic effect on gut epithelium and aggravate gut inflammation as seen in IBD. This insult to the epithelial barrier, in a genetically susceptible individual who is primed to create rapid inflammatory escalation at the gastrointestinal mucosa would rapidly amplify the initial Nightshade induced injury. A second possibility is that genetically predisposed individuals may experience a mast cell mediated true IgE allergic response to commonly cross reactive allergens in Nightshades such as LTPs and Profilin. However, rather than presenting with systemic allergy symptoms, increased Mast cell activity could be localized to the gut epithelium and present with GI upset. Thus, this increase in mast cell activity can potentially mediate worsening IBD and IBS symptoms.

Conclusion

Nightshade vegetables comprise a large family of plants with both a rich history of pharmacological potential as well as societal importance as food crops, including tomato, peppers, eggplant and white potato. Nightshade vegetables contain biologically active GA chemicals, including solanine and chaconine, which serve as plant defense mechanisms against predation but can potentially cause toxicity in humans when these crops are ingested as food. Furthermore, significant concentrations of these GAs in Nightshades have been shown to disrupt intestinal barrier integrity, increase colonic injury and inflammation in murine IBD models.

In addition to the biologically active GA molecules, Nightshades also contain common allergens including LTPs, Profilin, PPOs, and patatin that have been implicated in IgE mediated allergic reactions which include abdominal symptoms such as nausea, vomiting, and pain. In addition, potato Lectin has been shown to activate mast cells through

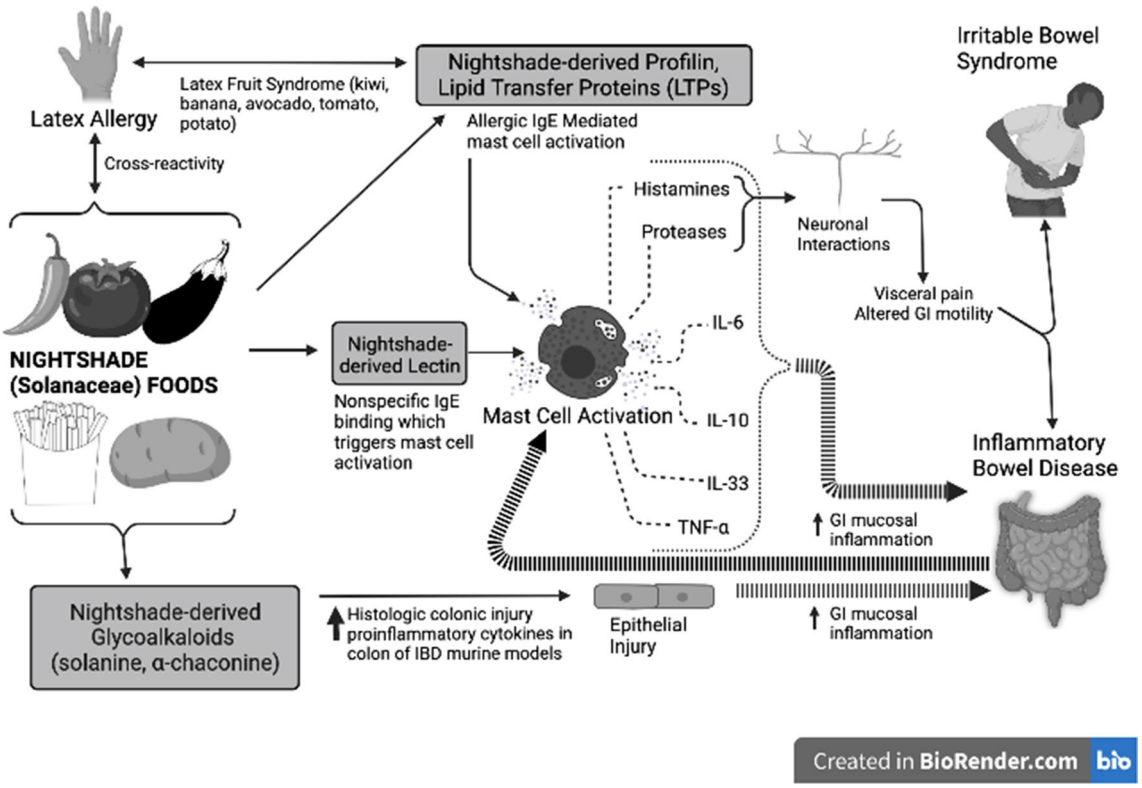

Fig. 2 Potential mechanisms of edible nightshade foods on irritable bowel syndrome and inflammatory bowel disease

IgE cross linking through a non-immunologically mediated mechanism. New insight in the mast cell biology of the gastrointestinal tract has linked activation of these cells with functional symptoms in patients suffering from IBS. Increased mast cell activation has also been found in the gut of IBD patients compared to controls. This evidence suggests Nightshades may be contributing to worsening clinical symptoms in IBD and IBS patients as a previously under-recognized dietary trigger and controllable environmental factor in clinical care.

Given that this is an extremely novel area of investigation, there are many limitations to the data presented. First and foremost, there have been no large scale human studies of Nightshade foods on gastrointestinal symptoms to date. The evidence on the effect of potato glycoalkaloids on IBD is based on animal studies and may have confounding variables such as the high fat content in fried potatoes. Future research is needed to assess for clinical response to Nightshade avoidance in IBD and IBS patients. This could be done with human cross over studies dietary exclusion studies comparing Nightshade avoidance with known therapeutic diets such as the low FODMAP diet. While mast cell activation is a promising pathophysiologic mechanism in IBD and IBS symptoms, there is a lack of systematic, large-scale, multi-center randomized controlled trials assessing its feasibility as a therapeutic target. Furthermore, the potential role of Nightshade vegetables in triggering mast cell degranulation will require additional investigation. Future studies will help determine if dietary guidance regarding Nightshade vegetable consumption will help IBD and IBS patients suffering from abdominal discomfort.

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Declarations

Competing interest The authors declare that they have no conflict of interest.

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