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Fermented noodles with degraded gluten (FNDG) improved digestion and gut motility in enteritis-induced mice

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Abstract Gluten proteins are key to developing a unique quality of flour because they confer viscosity, cohesiveness, and elasticity in the dough. However, gluten can impede digestion and absorption in gluten-sensitive individuals. In this study, enteritis was induced in mice with dextran sulfate sodium (DSS) salt. The mice later received a diet consisting of 3%, 12%, or 30% fermented noodles with degraded gluten (FNDG) or 30% normal noodle flour for 8 weeks. FNDG did not alter the growth performance or body composition. However, FNDG resulted in increased amylase activity in a dose-dependent manner (p<0.001), and it also improved the digestive capacity. FNDG at 30% concentration increased the level of gastrin (p<0.01) implying increased gut motility. The serotonin receptor levels were significantly reduced by FNDG at 12% (p<0.05) and 30% (p<0.01) concentrations. These findings indicate that a diet containing FNDG could help in the recovery from intestinal inflammation with improving digestive ability and gut motility. Overall, the inclusion of degraded gluten in the diet was found to enhance digestion, gut motility, and absorption in mice.

Keywords: enteritis, fermented noodle with degraded gluten, gluten, gut motility

Introduction

Gluten is an insoluble rubbery mass isolated by kneading flour dough and washing away starch granules and other water-soluble constituents with a dilute salt solution (Krull and Inglett, 1971). The dry rubbery mass can be composed of approximately 75-85% protein and 5-10% lipids (Wieser, 2007). Practically, the term 'gluten' refers to the protein fraction of the rubbery mass, which forms major structural protein complexes in some cereal grains (Laparra and Sanz, 2010). Proteins are stored together with starch in the endosperm of cereal grains such as wheat, rye, oats, and barley (Dahinden *et al.*, 2001). Gluten contains various proteins present in different forms as monomers or, with disulfide bond linkages, as oligomers or polymers (Nellesen *et al*., 2013). Gluten proteins have generally been classified based on their solubility in alcohol-water solutions; gliadin is soluble and glutenin insoluble. Gliadin and glutenin are the major sub-fractions of gluten and are key in developing the unique quality of flour because they confer water absorption capacity, viscosity, cohesiveness, and elasticity to the dough (Wieser, 2007).

Gluten can cause and aggravate nutritional health problems such as non-celiac gluten sensitivity (NCGS), gluten sensitive enteritis, and inflammatory bowel disease (IBD) (Limketkai *et al*., 2018). Glutamines and prolamines in gluten proteins are incompletely digested by pancreatic, brush border, and gastric peptidases, resulting in 33 amino acid long peptide residues (Shan *et al*., 2002). These peptides are absorbed through the intestinal epithelial barrier into the blood, triggering an immune response in gluten sensitive individuals (Visser *et al*., 2009). Gluten exposure to the small intestine in gluten sensitive individuals also induces inflammation, resulting in destruction of the villi and reduced crypt depth (Troncone and Jabri, 2011). The destruction of villi consequently leads to malabsorption of essential nutrients in the small intestine. Various critical symptoms caused by malabsorption, such as bloating, abdominal pain, diarrhea, and weight loss, are reported in patients with NCGS (Ford, 2009). Larazotide acetate and an oral combination of endopeptidase with endo-protease have been developed for detoxification of ingested gluten, but these are not significantly effective (Lebwohl *et al*., 2015). Lifelong abstinence from gluten-containing diets in NCGS and IBD patients can normalize the adverse symptoms within four weeks on average (Fasano and Catassi, 2001). Lactobacilli and fungi produce peptidases and proteases that degrade gluten and have been used for the manufacture of bread with a gluten concentration <20 ppm (Rizello *et al.,* 2007). Fermentation of gluten-containing flours in the manufacture of rye bread or pasta makes them tolerable to IBD and NCGS patients by reducing gluten content and/or prolamine epitopes (Rizello *et al*., 2007). Thus, the reduced gluten in diets through fermentation is expected to positively impact the health of gluten sensitive patients.

Therefore, in this study, the beneficial effects of fermented noodles with degraded gluten (FNDG) on digestion and gut motility were investigated after inducing enteritis in mice.

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Specifically, growth performance, body composition, digestive enzymes activity, and hormonal and neuronal regulation of motility were examined *in vivo*.

Material and Methods

Animals and treatments

FNDG was kindly provided from DongSung Foods (Yongin, Korea). FNDG was prepared by fermenting noodles with *Lactobacillus paracasei* that producing gluten-degradable enzyme thereby degrading gluten in noodle.

C57BL/6 male mice (4-weeks-old) were purchased from Daehan Bio (Eumseong, Korea) and housed in a controlled environment with temperature maintained at 22±1°C, a relative humidity of 50±10% and a light/dark cycle of 12 h. All mice were fed a standard chow diet *ad libitum* (Envigo Teklad Diets, Madison, WI, USA). After 2 weeks of adaptation, mice were randomly allocated to five groups (n=12 per group). In one group, untreated mice were provided with tap water and a normal chow diet. The other four groups were given 5% dextran sulfate sodium (DSS) in drinking water for one week; during this period, body weight was measured daily.

After inducing enteritis, the four groups were provided experimental diets formulated with different proportions of FNDG flour or a control diet of normal noodle flour for 8 weeks. The formula of experimental diets was based on the nutritional compositions of AIN93-G and designed to contain 30% gluten or gluten-free noodle powder. The five groups were as follows: untreated group (UT; no DSS+normal chow diet), control diet (CTL; DSS+30% normal noodle flour (w/w dry matter)), FNDG 3% (3% FNDG+27% normal noodle flour), FNDG 12% (12% FNDG+18% normal noodle flour), and FNDG 30% (30% FNDG). Body weight and feed intake data were collected weekly. The protocol for animal use was approved by the Institutional Animal Care and Use Committee (IACUC) at Kookmin University (KMU-2017-2).

Body composition

Mice were fasted overnight and then anesthetized with an intraperitoneal injection of ketamine (100 mg/kg bw) and xylazine (10 mg/kg bw). The body fat mass and lean mass were measured by dual-energy X-ray absorptiometry (DEXA) (Medikors Inc. Seongnam, Korea) at the end of the experiment.

Pancreatic digestive enzyme activity

Enzymatic activities of amylase, protease, and lipase were quantified from the pancreas. The tissues were homogenized with a bullet-blender in 1 mL phosphate-buffered saline (PBS) and centrifuged at 5,000 g for 5 min at 4°C. The supernatants were then transferred and used to measure the pancreatic enzyme activities using a commercial Sandwich-ELISA kit (Elabscience Biotechnology Inc., Houston, TX, USA). In brief, the procedure involved addition of serum samples and standard solution into a 96-well plate. Firstly, 100 μL of biotinylated detection antibody was added, incubated at 37°C for 1 h. An HRP-conjugated working solution was added and incubated at 37°C for 30 min. After the incubation in substrate reagent, a stop solution was added. The optical density was measured at 450 nm using a microplate reader (BioTek Instruments, Inc., Winooski, VT, USA). The absorbances obtained were compared against that of the prepared standard using a four-parameter logistic curve equation.

Peptide YY and gastrin

The levels of serum peptide YY and gastrin were measured using commercial ELISA kits (Elabscience Biotechnology Inc.). The experimental protocol provided by the manufacturer was followed. In brief, serum samples were added to a provided 96-well plate and incubated at 37°C for 90 min. Then, a biotinylated detection antibody, an HRP-conjugated solution, and a stop solution were added. Optical density was measured at 450 nm, and a four-parameter logistic curve equation was used to compare the substrate reagent value against a prepared standard.

Serotonin and dopamine receptors

Serotonin receptor (5-HT_4) and dopamine receptor (D2DR) levels were determined from the ileum sections of the small intestines using western blot analysis. Tissues were homogenized in RIPA buffer using a rotator for 50 min at 4°C, and the lysates were centrifuged at 5,000 g for 15 min at 4°C. The total protein concentrations for all samples were measured using a Bradford assay. Proteins were separated in 10% SDS-PAGE and transferred to polyvinylidene fluoride (PVDF) membranes. The membranes were then blocked using 5% BSA to avoid non-specific binding of primary antibodies. Blocked PVDF membranes were incubated with primary antibodies diluted 1:1000. The primary antibodies for $5HT_4$ (Abcam, Cambridge, UK), dopamine (D2DR) (Santa Cruz Biotechnology, Santa Cruz, CA, USA), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were used. Blots were then incubated in specified secondary antibodies (1:3000) at room temperature for 60 min and washed 4 times with TBST for 15 min. Blot proteins were visualized and quantified using Image Lab (Bio-Rad, Hercules, CA, USA).

Statistical analysis

Data are presented as the mean±standard error. Statistical analysis was performed using Prism 6 (GraphPad Software, San Diego, CA, USA). The differences of FNDG diets-fed mice against control were determined using one-way analysis of variance (ANOVA), followed by Dunnet's multiple comparison test. Group mean differences were considered to be statistically significant at $p<0.05$.

Results and Discussion

Body composition and feed intake

Enteritis was induced in mice by providing water containing 5% DSS for 1 week, and the body weight of mice was determined. We confirmed the induction of enteritis by hemafecia and a significant reduction in body weight compared with the UT group ($p<0.05$, Table 1). After 8 weeks of FNDG diets, growth

Table 1. Growth performance, body composition, and food intake of mice fed various inclusion ratios of fermented noodles with degraded gluten (FNDG) in the diet based on the air-dry weight

Group	UT	CTL	FNDG 3%	FNDG 12%	FNDG 30%
Initial body weight (g)	22.32±0.44*	17.03±0.24	16.94±0.28	17.02±0.24	17.09±0.23
Final body weight (g)	28.05±0.67	28.63±0.37	29.38±0.46	28.69±0.44	28.87±0.65
Food intake (g/week)	22.28±0.48	23.03±0.40	23.87±0.60	22.83±0.71	22.92±0.37
Weight gain (g/week)	0.72±0.14	1.42±0.34	1.53±0.47	1.11±0.23	1.45±0.35
Lean mass (%)	22.20±0.42	23.00±0.19	23.86±0.54	22.87±0.31	23.39±0.40
Body fat mass (%)	15.42±0.57	16.31±0.50	15.69±0.54	15.44±0.68	15.54±0.45

UT, positive control not treated with 5% DSS and fed a chow diet; CTL, 30% (w/w) normal noodle flour; FNDG 3%, 3% FNDG+27% normal noodle flour; FNDG 12%, 12% FNDG+18% normal noodle flour; and FNGD 30%, 30% FNDG. The asterisk indicates statistically significant difference from CTL at $p<0.05$. Data are expressed as the mean±standard error.

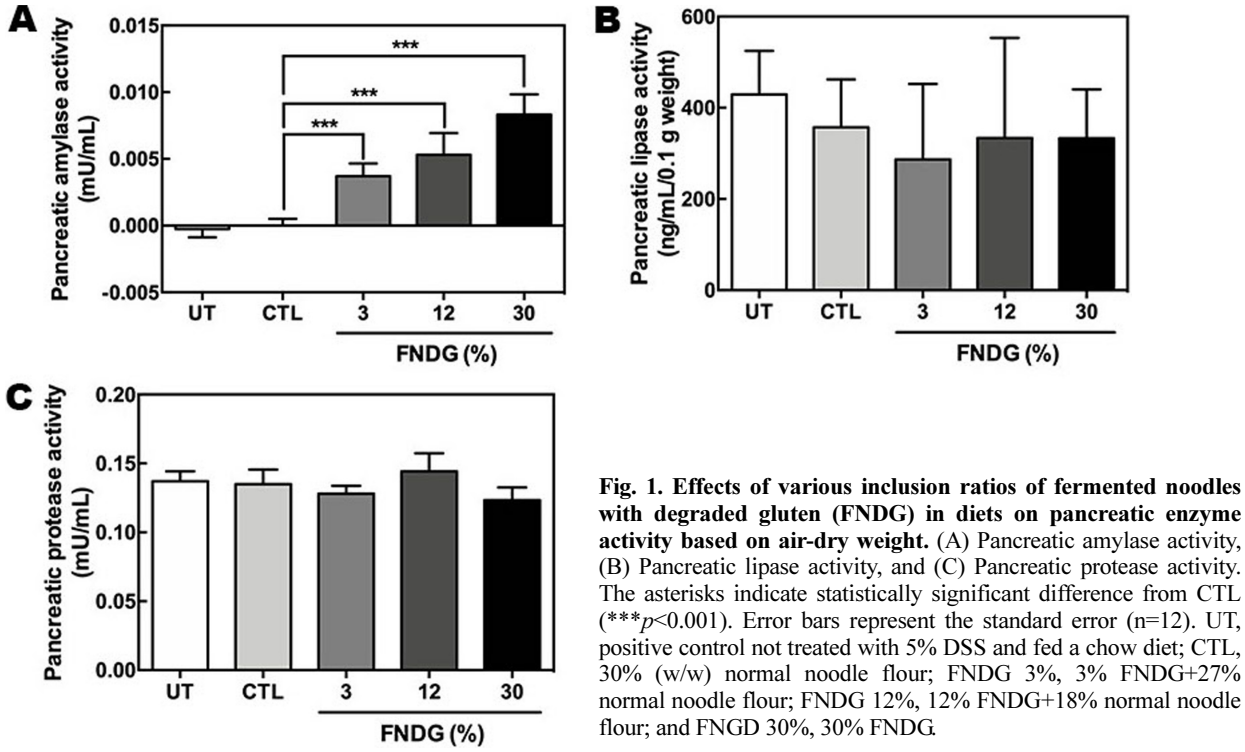

Fig. 1. Effects of various inclusion ratios of fermented noodles with degraded gluten (FNDG) in diets on pancreatic enzyme activity based on air-dry weight. (A) Pancreatic amylase activity, (B) Pancreatic lipase activity, and (C) Pancreatic protease activity. The asterisks indicate statistically significant difference from CTL (***$p<0.001$). Error bars represent the standard error (n=12). UT, positive control not treated with 5% DSS and fed a chow diet; CTL, 30% (w/w) normal noodle flour; FNDG 3%, 3% FNDG+27% normal noodle flour; FNDG 12%, 12% FNDG+18% normal noodle flour; and FNGD 30%, 30% FNDG.

performance, including body weight, weight gain, and feed intake, was measured. The UT group had a significantly higher initial body weight compared to the 5% DSS-treated groups ($p<0.05$), implying a successful induction of enteritis. FNDG altered neither final body weight, food intake, nor weight gain. Likewise, Funda *et al*. reported no significant differences in the body weight of mice fed a gluten-free diet or a chow diet (Funda *et al.*, 1999).

Lean mass and fat mass were investigated further by DEXA (Medikors Inc.), a body composition analyzer. There was no observed evidence that FNDG has an effect on body composition. It can, therefore, be assumed that FNDG appears not to substantially modulate body weight or fat mass in regular diet-based studies. Taken together, our findings suggest no significant differences in growth performance and body composition based on glucose intake.

Pancreatic digestive enzymes

Pancreatic amylase, lipase, and protease are essential for digestion of carbohydrates, fats, and proteins, respectively, and their activities are a good index for measuring the digestive capacity (Mahdavi *et al.*, 2018). The concentration of pancreatic amylase was significantly increased by FNDG supplementation in a dose-dependent manner ($p<0.001$) (Fig. 1A). On the other hand, lipase and protease levels were not significantly different in all FNDG-supplemented groups compared to the control group (Fig. 1B-C). It was not possible to dissect the pathway in which pancreatic amylase was increased by FNDG in this study. A possible explanation could be that the fermentation process increased the digestion of fiber, leading to greater availability of carbohydrates *in vivo*. Further research is required to better understand how FNDG is associated with improved pancreatic amylase activity.

Gastrin and peptide YY (PYY) hormones

Gastrin is a trophic hormone that stimulates the secretion of gastric acid from parietal cells of the stomach, and influences gut motility by increasing the release of acetylcholine in the ileum

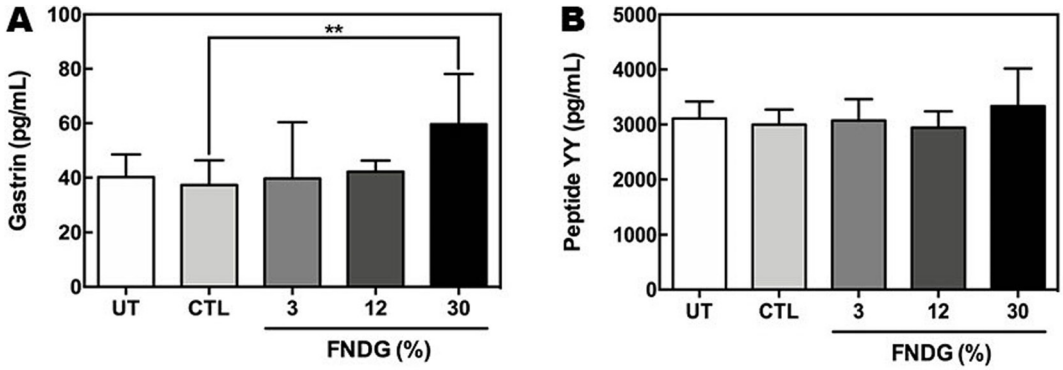

Fig. 2. Effects of various inclusion ratios of fermented noodles with degraded gluten (FNDG) in diets on gastrin and peptide YY hormone levels in serum based on air-dry weight. (A) Serum gastrin levels and (B) Serum peptide YY levels. The asterisks indicate statistically significant difference from CTL (*p<0.05 and **p<0.01). Error bars represent the standard error (n=12). UT, positive control not treated with 5% DSS and fed a chow diet; CTL, 30% (w/w) normal noodle flour; FNDG 3%, 3% FNDG+27% normal noodle flour; FNDG 12%, 12% FNDG+18% normal noodle flour; and FNGD 30%, 30% FNDG.

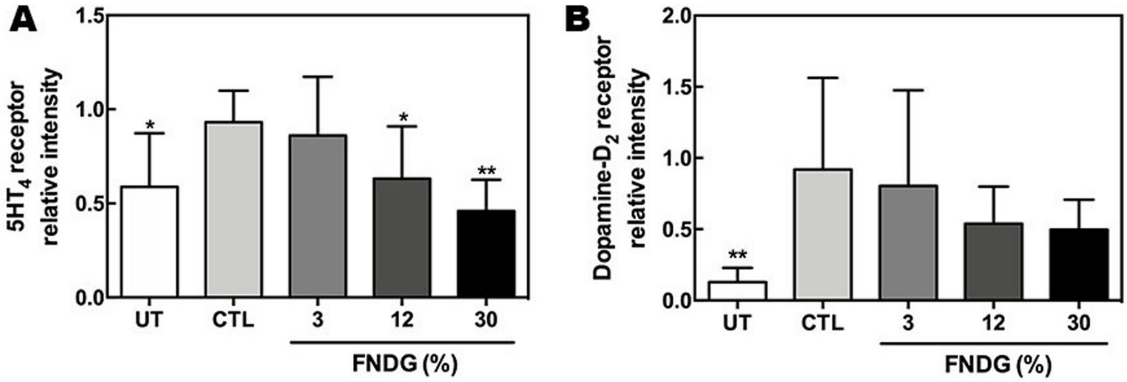

Fig. 3. Effects of various inclusion ratios of fermented noodles with degraded gluten (FNDG) in diets on the ileal serotonin receptors ($5HT_4$) and dopamine-D_2 receptors of the small intestines based on air-dry weight. (A) Serotonin receptor levels and (B) Dopamine receptor levels. The asterisks indicate statistically significant difference from CTL (*p<0.05 and **p<0.01). Error bars represent the standard error (n=12). UT, positive control not treated with 5% DSS and fed a chow diet; CTL, 30% (w/w) normal noodle flour; FNDG 3%, 3% FNDG+27% normal noodle flour; FNDG 12%, 12% FNDG+18% normal noodle flour; and FNGD 30%, 30% FNDG.

(Vizi *et al*., 1973). Healthy gut motility is essential for transit of feces and is remarkably deteriorated in conditions with impaired gut function such as enteritis and celiac disease (Nellesen *et al*., 2013). Linnestad *et al.* reported a reduction in gastrin release in celiac disease patients who had removed gluten from their diets and showed marked mucosal regeneration (Linnestad *et al.*, 1983). However, other studies have reported that gluten intake did not correlate with gastric acid secretion or serum gastrin level in patients with dermatitis herpetiformis (Andersson *et al.*, 1984; Kastrup *et al.*, 1985). In this study, gastrin level was not significantly different between the positive control UT and the CTL. However, 30% FNDG gastrin level was significantly increased (p<0.01) compared to the control group (Fig. 2A). This might imply improved gut motility even for individuals considered to be in a healthy state if they consume 30% FNDG in their diets.

PYY is a short peptide hormone released from the ileum and colon in response to food consumption, and it reduces appetite. This hormone also mediates the feedback inhibition of gastric acid secretion, gastrointestinal motility, and pancreatic enzyme output (Wahab *et al.*, 2001). Changes in PYY seem to be an adaptive response to alterations in pathophysiological conditions from disease (El-Salhy *et al.*, 2013). In this study, no significant differences were noted in PYY level among the groups compared to the control (Fig. 2A). Elevated level of PYY, which was reduced to normal level within 8 months on a gluten-free diet, have been reported in CD patients (Sjölund and Ekman, 1988). In another study on patients with CD, the level of PYY was consistent with that of the control before and after withdrawal of gluten (Linnestad *et al.*, 1983). These results are consistent with our observations in the present research, which showed that consumption of a gluten-free diet had no influence on PYY level (Fig. 2B). FNDG intake, therefore, does not influence appetite or feed intake, as presented in Table 1.

Serotonin and dopamine receptors

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter secreted by the gastrointestinal tract. It regulates the sensation and motility of the gastrointestinal tract through various receptors including 5-HT_3 and 5-HT_4 (Avena *et al.,* 2008). 5-HT has been recognized as an important signaling molecule in the gut, although its exact functions are not fully understood. 5-HT exerts non-conventional actions such as promoting inflammation and serving

as a trophic factor to maintain and promote the development of neurons (Mawe and Hoffman, 2013). However, other than the non-conventional actions of 5-HT, 5-HT_4 receptor agonists have been used to treat functional disorders like diarrhea or constipation (Mawe and Hoffman, 2013). Studies from 5-HT_4 knockout mice indicated a postnatal reduction in enteric neurons, and treatment of adult mice with 5-HT_4 agonists promoted the generation of new enteric neurons (Gershon, 2013; Liu *et al.*, 2009). It is not understood whether 5-HT signaling changes in response to altered gut function. However, some evidence supports the concept that altered 5-HT signaling can lead to changes in gut function (Mawe *et al.*, 2006). In this study, UT, FNDG 12%, and FNDG 30% had significantly lower levels of 5-HT_4 compared to the CTL ($p<0.05$, $p<0.05$, and $p<0.01$, respectively) (Fig. 3A). The decrease in 5-HT_4 occurred in a dose-dependent manner. The 5-HT_4 level of the UT group can be considered to be the healthy baseline because they did not receive 5% DSS administration. Therefore, a significant decrease in 5-HT_4 receptor level after FNDG treatment, which matched that of the UT group, must be a positive response induced by FNDG to reduce intestinal inflammation after 5% DSS administration.

Dopamine acts as an antagonist of serotonin and inhibits gastrointestinal motility through suppressing the release of acetylcholine from cholinergic neurons. Blocking dopamine receptors can prevent dopamine action through liberation of acetylcholine (Avena *et al.,* 2008). The UT group had significantly low level of dopamine-D_2 receptors ($p<0.01$) compared to the CTL (Fig. 3B). All mice that had induced enteritis showed increased level of dopamine-D_2 receptors compared to the UT group. However, FNDG-containing feed reduced the level of dopamine-D_2 receptors in a dose-dependent manner even though the differences did not reach statistical significance (Fig. 3B). This evidence suggests that increased degraded gluten in the diet could reduce dopamine-D_2 receptors to increase gut motility.

Conclusion

In this study, the intake of FNDG-containing feed by mice with a history of induced enteritis led to improved digestive ability signified by increased pancreatic amylase activity. Increased gastrin secretion due to FNDG treatment led to improved gut motility, which is a well-documented phenomenon. The observed decrease in serotonin receptors suggested that FNDG had the beneficial effect of reducing gastrointestinal inflammation after induction of enteritis using 5% DSS. The reduction of gastrointestinal inflammation must have subsequently resulted in improved absorption. However, further studies are required to research the behavior of serotonin and dopamine receptors when diets with degraded gluten are fed to mice. The increased inclusion of degraded gluten might also yield positive results in future studies.

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