Systematic review of the role of oat intake on gastrointestinal health

Ezra Valido[1,2]*, Jivko Stoyanov[1]*, Alessandro Bertolo[1], Anneke Hertig-Godeschalk[3], Ramona Maria Zeh[1], Joelle Leonie Flueck[3], Beatrice Minder[4], Stevan Stojic[2], Brandon Metzger[5], Weston Bussler[5], Taulant Muka[4], Hua Kern[5]¥, Marija Glisic[1,4]¥

[1]Swiss Paraplegic Research, Nottwil, Switzerland

[2]Department of Health Sciences, University of Lucerne, Lucerne, Switzerland

[3]Institute of Sports Medicine, Swiss Paraplegic Centre, Nottwil, Switzerland

[4]Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland

[5]Standard Process Nutrition Innovation Center, Kannapolis, NC 28018, USA

*denotes equal contributions
¥ certifies that both authors are considered last authors to all academic and professional effects, and that their names can be legitimately swapped in their respective publication list.

Corresponding Author:

Ezra Valido, MD, MPM, MPH

Swiss Paraplegic Research, Nottwil, Switzerland

Email: ezra.valido@paraplegie.ch

Phone: +41 41 939 66 39

Number of Word Count: 5047/5000

Number of Figures: 2

Number of Tables: 2

Supplementary data:

Supplemental Appendix I: Full search strategy per database for the systematic review for oat and gastrointestinal health; Supplemental Table 1. Characteristics of randomized controlled trials with oat intake conducted in individuals without gastrointestinal diseases; Supplemental Table 2: Characteristics of non-randomized trials on oat intake conducted in individuals without gastrointestinal diseases; Supplemental Table 3: Characteristics of randomized controlled trials with oat intake conducted in individuals with celiac disease and ulcerative colitis; Supplemental Table 4. Characteristics of non-randomized trials conducted in individuals with celiac disease and ulcerative colitis; Supplemental Table 5. Characteristics of observational studies with oat intake conducted in individuals with celiac disease and Crohn's disease; Supplemental Table 6. Characteristics of in vitro studies with oat conducted in individuals with celiac disease; Supplemental Table 7. Characteristics of in vitro studies

with oat conducted in individuals without gastrointestinal diseases; Supplemental Table 8. Quality assessment of randomized controlled trials with oat intake using the Risk of Bias tool for RCT; Supplemental Table 9. Quality assessment of observational studies with oat intake using Newcastle-Ottawa rating scale; Supplemental Table 10. Risk of bias assessment of the non-randomized trials with oat intake based on the National Heart Lung and Blood Institute. Quality Assessment Tool for Before-After (Pre-Post) Studies; Supplemental Table 11. Risk of bias assessment of the non-randomized trials with oat intake based on the National Heart Lung and Blood Institute Quality Assessment Tool; Supplemental Table 12. Quality assessment of in vitro with oat studies using the Toxicological data Reliability Assessment Tool

Running Title: Oat and gastrointestinal health

List of Abbreviations:

GI   Gastro-intestinal

CeD   Celiac disease

UC   Ulcerative colitis

IBS   Irritable Bowel Syndrome

IBD   Inflammatory Bowel Disease

RCT   Randomized Controlled Trial

SCFA   Short Chain Fatty Acid

PRISMA   Preferred Reporting Items for Systematic Review and Meta-Analysis

TMAO   trimethylamine oxide

RoB   Risk of Bias

ToxRTool   Toxicological data Reliability Assessment Tool

GFD   Gluten-free diet

CH$_4$ Methane

GSRS   Gastrointestinal Symptom Reporting Scale

tTG   tissue Transglutamase

IEL   Intraepithelial lymphocytes

IL   Interleukin

NK   Natural killer

TGF   Transforming growth factor

Treg   Regulatory T cell

IFN   Interferon

EmA   Anti-endomysial antibody

1   **ABSTRACT**

2   Background: Oats are a food source with multiple health benefits that could support

3   beneficial bacterial groups and provide important bioactive compounds for the gut.

4   Objective: This review explores the association between oat intake, gastrointestinal

5   (GI) symptoms and microbial community changes in individuals with celiac disease

6   (CeD), irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) and

7   without GI disease.

8   Methods: Four databases and Google Scholar were systematically searched from

9   inception until April 29, 2021. Clinical trials, observational studies and *in vitro* studies

10   with human gut derived samples were included.

11   Results: There were 84 articles (23 RCTs, 21 non-randomized trials, 8 observational

12   and 32 *in vitro* studies) included. Oat intake increased total bacterial count, *Lactobacilli*

13   *spp.* and *Bifidobacterium spp* in healthy individuals and those with CeD*.* There was an

14   increased concentration of short chain fatty acids and improved gut permeability with

15   oat intake but with no significant quality of life difference. In some individuals with CeD

16   consumption of certain oat types was associated with worsening of GI symptoms. We

17   found no studies reporting on IBS and only 3 for IBD. The quality of RCTs showed

18   some concerns mostly in domains of randomization (73.9%) while the quality of

19   evidence of non-RCTs, observational and *in vitro* studies was satisfactory.

20   Conclusion: Oat intake was associated with the increase of beneficial bacterial groups

21   in individuals without GI disease and those with CeD. The majority of studies showed

22   no changes in GI symptoms with oat consumption. *In vitro* studies in CeD provide

23   insight to oat sensitive individuals and their GI mucosa but the clinical studies remain

24   limited, precluding our ability to draw firm conclusions. The prevalence of oat sensitivity

25   in individuals with CeD should be further explored as this could improve clinical

26   management and facilitate inclusion of oat in the diet for this population.

27 **Key Words**: Oat; Oat Bran; Gastrointestinal symptoms; Microbiome; Celiac disease

28

29 **1. INTRODUCTION**

30

31 Oats (*Avena sativa*) are a valuable food source known for multiple health benefits.

32 They provide substantial amounts of carbohydrates including soluble fibers and other

33 bioactive compounds (1) that have been associated with benefits in lowering the risks

34 for obesity (2), cardiovascular diseases (3), type 2 diabetes (4) and gastrointestinal

35 (GI) diseases (5). The intake of oat dietary fibers can delay gastric emptying and affect

36 absorption of nutrients and the motility in the small bowel (6). Oat intake can affect the

37 gut microbiome by supporting the growth of beneficial bacterial groups (7) thus

38 contributing to improved GI health profile.

39

40 Gut dysbiosis has been linked with development or progression of various GI

41 conditions such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD),

42 celiac disease (CeD) and GI cancer (8-12). The bacterial population dynamics are

43 dependent on available substrates in the gut. The balance of beneficial and pathogenic

44 bacterial groups depends on food intake, the individual's sex, age and co-morbidities

45 (13). Bacterial fermentation in the colon produces beneficial metabolites such as short

46 chain fatty acids (SCFAs) that are associated with favorable health outcomes in

47 metabolic disorders (14), inflammatory bowel disorders and colon cancer (15). SCFAs

48 are an energy source for gut epithelial cells and promote tightening of cell junctions,

49 improvement of gut mucosal barrier, support optimal colon pH and help control the

50 growth of microorganisms (16). Among the SCFAs, butyrate is the preferred energy

51 source by colonic cells and has anti-inflammatory properties (17, 18). Most bacteria

52 can produce acetate but only specific bacteria produce propionate or butyrate (19).

53 Emerging evidence has suggested that increasing the absolute number or the

54 proportion of *Lactobacilli* and *Bifidobacteria*, can be used as a success marker for

55 interventions targeting healthy GI microbial populations (20).

56

57 Previous systematic reviews and a meta-analysis on oat intake and the intestinal health

58 have been focused on the safety of oats by individuals with bowel disorders (3, 21-23).

59 Their results have outlined that oats are a valuable source of nutrients without gut

60 inflammation but other aspects such as non-inflammatory associated symptoms and

61 the benefits of modulating the gut microbiome have not been studied. Likewise, the

62 effects of the oats on the microbiome not only in individuals with GI disorders but also

63 the general population are lacking in these reviews. Thus, our systematic review aims

64 to summarize and explore the evidence on the effect of oat intake on the GI health and

65 the gut microbiome changes in individuals with (CeD, IBD, IBS) and without GI

66 conditions.

67

68 **2. METHODS**

69

70 *2.1 Data Sources and Search Strategy*

71 This review was conducted in accordance with the workflow presented by Muka et al.

72 (24) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

73 Statement (PRISMA) (25) guidelines. Four electronic databases were systematically

74 searched: EMBASE (Elsevier, Netherlands), MEDLINE (National Library of Medicine,

75 US), Cochrane central (Cochrane Collaboration, UK) and Web of Science (Thomson

76 Reuters, US) from inception until April 29th 2021 and additionally the first 200 results

77 were downloaded from the Google Scholar search engine. The detailed search

78 strategy is provided in the **Supplemental Appendix I**.

79

80   *2.2 Study Selection, Eligibility Criteria and Data Extraction*

81   Detailed inclusion and exclusion criteria can be found in the review protocol

82   (PROSPERO ID CRD42020190484). In brief, *in vitro* studies, observational studies,

83   randomized controlled trials (RCT) and non-randomized trials were eligible for

84   inclusion if they: (i) were conducted among individuals of any age without GI conditions

85   or with IBD, IBS or CeD and (ii) investigated associations of oat, oat β-glucan and

86   avenanthramides with any of the following outcomes: (a) digestive symptoms: bloating,

87   abdominal pain, diarrhea, constipation, bowel inflammation, mucosal villus damage,

88   (b) GI conditions: IBD, IBS or CeD focusing on risk of developing a disease and

89   changes in the course of the disease management and/or (c) gut microbiome: changes

90   in gut permeability, bacterial diversity, gut dysbiosis, gut microbiota metabolites and

91   markers [SCFAs and trimethylamine oxide (TMAO)].

92   Due to the nature of our research question and complexity of the topic studied, to

93   facilitate the interpretation of our findings, we excluded animal studies and studies

94   including participants with GI cancers. In addition, letters to the editor, reviews,

95   commentaries and conference abstracts were excluded. Titles and abstracts were

96   independently evaluated by two reviewers and the full-texts were assessed by two

97   independent reviewers. Disagreement was settled by reaching a consensus or by

98   consulting a third reviewer. Two authors independently extracted the relevant

99   information using a pre-defined data extraction form.

100   *2.3 Methodological Quality Assessment*

101

102   The quality of RCTs was assessed by two independent reviewers using the Risk of

103   Bias tool for RCT (Rob2.0) (26). Quality of controlled and one arm non-randomized

104   trials was evaluated using the National Heart Lung and Blood Institute Quality

105   Assessment Tool (27, 28). Observational studies were evaluated using the Newcastle-

106   Ottawa Scale (29). Reliability of experimental studies was evaluated using the

107   Toxicological data Reliability Assessment Tool (ToxRTool) (30).

108

109   **3. RESULTS**

110

111   *3.1 Literature search and study characteristics*

112

113   There were 5,199 citations identified, with 119 selected for full-text evaluation (**Figure**

114   **1**). Of those, 84 articles (23 RCTs, 21 non-randomized trial, 8 observational and 32 *in*

115   *vitro* studies using human material) comprised 4,022 participants (**Table 1**). Among

116   observational and clinical studies, nine studies (17.3%) were conducted in healthy

117   individuals, eight (15.4%) were conducted in the elderly and individuals with underlying

118   conditions (i.e. hyperlipidemia, glucose intolerance), three (5.8%) were with IBD and

119   31 (59.6%) were in individuals with CeD. Among the *in vitro* studies, most were done

120   using specimens from healthy individuals (n=24, 75%) and eight studies conducted

121   using specimens from CeD. There were 10 (19.2%) observational/clinical studies and

122   three *in vitro* studies (9.4%) conducted among pediatric populations. Detailed

123   characteristics of the included studies can be found in **Supplemental Tables 1-7**.

124

125   <Insert Figure 1>

126   <Insert Table 1>

127

128   *3.2 Oat intake and changes in gut microbiome*

129

130   We identified nine RCTs, four non-randomized trials, one observational and 25 *in vitro*

131   studies that provided information on how oat intake or experimental supplementation

132   may affect either gut microbiome or SCFAs. Among the RCTs, three were conducted

133   in healthy individuals, four in glucose-intolerant or type 2 diabetes and adults with

134   elevated cholesterol, one in a pediatric population with CeD and one with adults with

135   ulcerative colitis (UC). The intervention duration ranged from three weeks to 52 weeks

136   and interventions (e.g. whole grain oat granola, ropy based oat and fermented oat) and

137   controls (gluten-free diet [GFD], condensed milk, placebo) were heterogeneous

138   between the included studies (**Table 2**, **Supplemental Table 1**). There was a general

139   increase in total bacterial count and the count of *Lactobacilli spp.* and *Bifidobacterium*

140   *spp*. after the oat-based intervention across different RCTs (31-37).

141

142   <Insert Table 1>

143

144   In an RCT among healthy individuals, the group receiving 3g of oat fermented in

145   *Lactobacillus plantarum* over a period of three weeks had increased total SCFAs,

146   acetic and propionic and lactic acids at the end of the study, compared to baseline.

147   The placebo group (pure rose hip drink) only had lactic acid increased. Differences

148   between the two groups were not explored (33). In another cross-over RCT with

149   metabolic disorders, after a six-week intervention, when two supplementation periods

150   (whole grain oat granola versus non- whole grain breakfast) were compared,

151   differences in SCFAs were not reported and no differences in SCFAs were found when

152   comparing baseline vs. end of study (33). In a trial that described fecal SCFAs patterns

153   in a pediatric population with newly diagnosed CeD, after being treated for a year with

154   GFD with or without oats, those treated with GFD-oats had significantly higher acetic

155   acid, n-butyric acid and total SCFAs concentrations after a year of dietary intervention

156   compared to the GFD group but no differences were observed between two groups at

157   0 and 6 months of intervention. The concentrations of propionic, i-butyric, i-valeric and

158   n-valeric acids did not differ between the study groups at 0, 6 and 12 months

159   respectively. During the year, the fermentation index, the amount of acetic acid minus

160   propionic acid and n-butyric acid divided by the total amount of SCFAs, remained high

161   in both the GFD-oats and the GFD groups with no significant differences (38). In

162   another RCT of adults with UC, the group with a daily intake of 60g of oats for 24 weeks

163   had total SCFAs, propionic acid, i-butyric acid, butyric acid and valeric acid significantly

164   increased when compared to those consuming low fiber wheat products (39). Findings

165   from non-randomized trials and an observational study are consistent with data from

166   RCTs on increased SCFAs(40-43) (**Supplemental Table 2, 5**).

167

168   We found 25 *in vitro* studies looking into oat fermentation and microbial metabolic

169   activity in fecal samples (**Supplemental Table 7**). In general across the studies, the

170   population of anaerobes decreased, Proteobacteria and Bacteroides phyla increased

171   and the populations of the Lactobacillaceae and Bifidobacteriaceae families increased.

172   Furthermore, increased levels of SCFAs and decreased production of proteolytic

173   markers were observed (35, 44-67).

174

175   The impact of oat on gut barrier integrity and intestinal permeability has been

176   demonstrated in *in vitro* settings wherein oat bran β-glucan improved gut barrier

177   integrity (65). Pham et al. (65) tested the effect of human gut microbial content with

178   five common dietary fibers (oat β-glucan 28%; oat β-glucan 94%; dried chicory root

179   containing inulin 75%; xylo-oligosaccharide; inulin 90%) and control – maltodextrin.

180 After fermentation the gut barrier integrity was measured using a Caco-2/HT29-MTX

181 cell lines co-culture model, mucus production HT29-MTX and HT29 cell models. The

182 supernatant from fermentation of all tested fibers led to increased transepithelial

183 electrical resistance suggesting increased junction strength between intestinal cells

184 with oat β-glucan 28% being the most effective in this model (65).

185

186 *3.3 Oat intake and GI symptoms*

187

188 We identified five RCTs and four non-randomized trials examining associations

189 between oat intake and GI symptoms among individuals without GI disease

190 (**Supplemental Table 1-2**). In a cross-over RCT comparing the effect of oat and wheat

191 cereal groups to reduce blood lipids in hypercholesterolemic adults, authors reported

192 significantly higher self-reporting of intestinal gas production, looser stools in oat bran

193 and higher frequency of constipation in wheat cereal group (68). In another RCT with

194 moderately hypercholesterolemic adults over a period of 8 weeks, intake of 3g of oat

195 β-glucan and oat-based isocaloric placebo without β-glucan did not exert any

196 significant unfavorable effect on the self-perceived intestinal well-being (69). In a 3-leg

197 crossover RCT among 14 healthy adults, different molecular weights of oat β-glucan

198 did not significantly increase GI symptoms but gender difference in pain experience

199 was observed (70). Conversely, in a RCT of 209 elderly residents in a nursing home,

200 consumption of fermented oat with *Bifidobacterium* significantly increased bowel

201 movements compared to placebo (71) while in a RCT of healthy pediatric individuals,

202 aged six months to three years old, consumption of fermented oat with *L. plantarum*

203 for three weeks was comparable to control (34). In a controlled non-RCT of 30 frail

204 inhabitants of a geriatric ward aged 57-100 years receiving either oat bran (fiber group)

205 or usual diet (control group) for 12 weeks, use of laxatives was reduced significantly at

206   59% for those taking oat bran with their body weight remaining constant (72). In

207   another single-arm trial, 50 elderly individuals with complaint of constipation were

208   entered into an open trial to assess the benefit on their symptoms by adding oat bran

209   biscuits ('Lejfiber') twice daily to their diet over a period of 12 weeks. Treatment

210   improved their bowel frequency, stool consistency and pain on defecation with no

211   participant complaining of side-effects (73). Another single-arm intervention study of

212   33 healthy children age 7-12 years old (15 female and 18 male) who reported ≤5 bowel

213   movements per week during screening consumed two servings of instant oatmeal daily

214   for 2 weeks(74). No differences in stool frequency or consistency were observed from

215   beginning and at the end of the trial (76). Kajs et al. (77) investigated whether a high

216   concentration of methanogens influences the host's response to ingestion of non-

217   absorbable, fermentable materials. Participants were placed on a basal diet (primarily

218   rice and hamburger) with minimal amounts of non-absorbable, fermentable substrate

219   and classified them as either high or low methane (CH_4) producers. After stabilization

220   of the breath gas excretion, the participants ingested either sorbitol or oat. Authors

221   found that low producers of CH_4 reported significantly increased bloating and cramping

222   after sorbitol ingestion and increased bloating after oat ingestion compared to high CH_4

223   producers. The reduced presence of methanogenic organisms has been associated

224   with reduced gut bloating and cramping (75).

225

226   Three RCTs, six non-randomized trials and five observational studies looked into

227   changes in GI symptoms with oat intake in individuals with CeD (**Figure 2**). These

228   studies generally aimed to explore the safety of using oats in addition to GFD

229   (**Supplemental Tables 3-7**). In a one-year RCT, the effect of oats-containing GFD on

230   quality of life and GI symptoms in individuals with CeD were compared to traditional

231   GFD. Quality of life did not differ between the groups but there were more GI symptoms

232   as assessed by the GI Symptom Rating Scale (GSRS) in the oats-consuming group.

233   The higher the GSRS the more the individual suffers from a GI symptom (76). The oats

234   group had significantly more diarrhea with a trend towards a more severe average

235   constipation symptom score and the severity of symptoms was not dependent on the

236   degree of intestinal inflammation (77). In a large crossover RCT evaluated the long-

237   term validity and safety of pure oats in the treatment of pediatric population with CeD

238   over a period of 15 months, a total of 306 pediatric individuals with CeD on a GFD for

239   less than two years were randomly assigned to eat specifically prepared GFD

240   containing an age-dependent amount of either placebo or purified non-reactive

241   varieties of oats for two consecutive 6-month periods separated by a washout standard

242   GFD for three months. GSRS scores were not different between the two groups in the

243   two treatment periods regarding absolute variations (78). In a RCT with adults with

244   CeD, large daily intake of 100g of kilned (heat sterilized) vs unkilned oats for 52 weeks

245   were compared, kilned vs unkilned oats were comparable in self-reported GI

246   symptoms (79).

247

248   <Insert Figure 2>

249

250   Results from the non-randomized trials generally show no harm (80-85) of adding oat

251   to GFD though two studies showed potential harms (80-85). Baker et al. (84)

252   investigated the effect of addition of oats and barley to GFD with individuals with CeD

253   using an oral 5g xylose excretion test to assess small bowel function before and after

254   intake. Both oats and barley were found to be potentially harmful to individuals with

255   CeD although barley had more toxic effect (84). On the other hand, 19 adults with CeD

256   on GFD were challenged with 50g of oats per day for 12 weeks and authors found that

257   oats were well tolerated by most patients but reports of initial abdominal discomfort

258 and bloating were observed (85). Among six observational studies with individuals with

259 CeD, there was no significant increase in GI symptoms in long term intake of oats (86-

260 91).

261

262 There was one RCT, one non-randomized trial and an observational study that looked

263 into GI symptoms and IBD. In a RCT among adults with UC who consumed 60g of oat

264 daily for 24 weeks, when compared to those with low fiber wheat products, the oat

265 group had significantly higher diarrhea in the 8th and 16th week but eventually were

266 comparable to the other group at the end of trial (39). In contrast, in a non-randomized

267 trial among adults with UC with 60g of oat bran added to their usual diet for 12 weeks,

268 no increase in GI symptoms was observed (42). In an observational study among

269 individuals with genetic risks for developing Crohn's disease, significantly low

270 consumption of oats, rye and bran played a role in influencing the GI microflora that

271 predisposed the onset of the disease (92).

272

273 *3.4 Oat supplementation and histopathological/immunological changes*

274

275 We identified 10 RCTs, 11 non-randomized trials, five observational studies and eight

276 *in vitro* studies exploring histological changes in the small intestines (i.e. intestinal villi

277 structure, number of intraepithelial lymphocytes [IELs]) or immunological effects of

278 oats (i.e. gliadin and reticulin antibodies) (**Supplemental Table 3,4,7**). Among

279 identified studies, the majority of studies were with individuals with CeD (23 in adult

280 and 11 in pediatric population) and those findings are summarized in **Figure 2.**

281

282 Among RCTs focusing on individuals with CeD, both in adults and pediatric populations

283 with newly diagnosed CeD or CeD in remission, neither worsening in the small intestine

284   morphology nor inflammation across diet groups (GFD including oats vs. conventional

285   GFD) were reported (78, 79, 93-97). In adults with CeD, two RCTs reported no

286   worsening of the autoimmune responses (77, 94). The toxicity of oats in a pediatric

287   population with CeD was studied by investigating either anti-avenin antibodies or IgA-

288   class autoantibody deposits targeted against jejunal transglutaminase 2 (TG2)- (a

289   potentially more sensitive disease marker than serum antibodies or conventional

290   histology). The majority of RCTs showed no worsening in these serology markers (78,

291   95-98). A single RCT compared paired small intestinal biopsies, before and after >11

292   months on a GFD, collected from pediatric population with CeD who were enrolled

293   either of two diets: standard GFD (GFD-std; n = 13) and non-contaminated oat-

294   containing GFD (GFD-oats; n = 15). Expression levels of mRNAs for 22 different

295   immune effector molecules and tight junction proteins were determined by quantitative

296   reverse transcriptase polymerase chain reaction (RT)-PCR. The number of mRNAs

297   that remained elevated was higher in the GFD-oats group. In particular, mRNAs for the

298   regulatory T cell (Treg) signature molecules interleukin-10 (IL-10) and transforming

299   growth factor-β1 (TGF-β1), the cytotoxicity-activating natural killer (NK) receptors

300   KLRC2/NKG2C and KLRC3/NKG2E, and the tight junction protein claudin-4 remained

301   elevated. Between the two groups, most significant differences were seen for claudin-

302   4 (P = 0.003) and KLRC3/NKG2E (P=0.04) (99).

303

304   In line with findings from RCTs, non-randomized trials and observational studies in

305   general supported no worsening in histopathology nor serological markers (80, 83, 85,

306   88, 89, 91, 100-105). On the other hand in the study of Hardy et al. (107), 73 individuals

307   with HLA-DQ2.5+ CeD consumed a meal of oats (100g/day over 3 days) to measure

308   the *in vivo* polyclonal avenin-specific T cell responses to peptides contained within

309   comprehensive avenin peptide libraries. Avenin-specific responses were observed in

310 6/73 (8%) HLA-DQ2.5+ CeD individuals against four closely related peptides. In the

311 same population, an oral barley challenge efficiently induced cross-reactive

312 avenin/hordein-specific T cells in most individuals with CeD, whereas wheat or rye

313 challenge did not. *In vitro*, immunogenic avenin peptides were susceptible to digestive

314 endopeptidases and showed weak HLA-DQ2.5 binding stability (106). Similarly, in a

315 non-randomized trial of 35 in a pediatric population with CeD, oats were tested for

316 immunogenecity and found that avenins derived from local Russian and foreign oat

317 varieties were able to induce immune response(107). Likewise, in an observational

318 study of Tuire et al. (86) oat intake was associated to persistent intraepithelial

319 lymphocytosis among individuals with CeD.

320

321 In an *in vitro* model, anti-endomysial antibodies (EMA) production was tested in

322 duodenal mucosa specimens collected from 13 individuals with CeD in remission.

323 EMAs were detected in specimens from all patients after the challenge with gliadin but

324 no EMAs were detected in any of the specimens cultured with avenin and its C fraction

325 (108). Similarly, in another study using duodenal mucosa samples from CeD

326 individuals, increased immunologic activities with expression of IFN-γ and IL2 in all

327 samples with gliadin were reported but no significant stimulation with avenin was

328 observed, suggesting that immunogenic sequences from gliadin are not present or

329 mimicked by avenin (109). Avenin *in sera* were compared in a pediatric population

330 with CeD and reference population in the study of Hollen et al. (110) and they showed

331 that antibodies against avenin (both IgG and IgA type) were developed with levels

332 correlating positively with those against gliadin and these levels were significantly

333 higher than in the reference population. Meanwhile in a study including nine adults with

334 CeD who had a history of oats exposure, authors found oats-avenin-specific and

335 reactive intestinal T-cell lines from three patients who did not tolerate oats and in two

336   other patients who appeared to tolerate oats. The avenin-reactive T-cell lines

337   recognized avenin peptides in the context of HLA-DQ2. These peptides have proline

338   and glutamine rich sequences resembling wheat gluten epitopes. Deamidation

339   (glutamine→glutamic acid conversion) by tissue transglutaminase was involved in the

340   avenin epitope formation. It has been suggested that the oat intolerance may be a

341   reason for villus atrophy and inflammation in patients with CeD who are eating oats but

342   otherwise are adhering to a strict GFD (111). In the study of Kilmartin et al. (112),

343   prolamins derived from wheat, barley, rye and oats were tested to see if they were

344   able to stimulate T cell lines (measured by (3) H-thymidine incorporation or cytokine

345   [IL-2, IFN-gamma]) proliferated from mucosal lesions of individuals with CeD. They

346   observed that all the prolamins are able to stimulate the T cell lines.

347

348   Three *in vitro* studies explored the immunogenicity of different oat varieties. Maglio et

349   al. (113) investigated the immunological and biological effects of *Avena genziana* and

350   *Avena potenza* among CeD individuals. The oat prolamin peptides were not able to

351   induce enterocyte proliferation, increase in IL-15, or increase in CeD25+ cells which

352   suggest that two oat varieties are safe for individuals with CeD (113). Similarly, Comino

353   et al. (114) studied oats from different cultivars from Spanish and Australian sources.

354   They reported a wide range of reactivity of oat cultivars to the anti-33-mer G12 and the

355   reactivity of isolated celiac T cells to oat varieties ranged from none to maximal G12

356   monoclonal antibodies (114). In another study, Silano et al. (115) studied three oat

357   cultivars (cv. Irina, cv. Potenza e cv. Nave) in activating the gliadin-induced TG2-

358   dependent events in pediatric individuals with CeD. The Nave oat cultivar elicited

359   K562(S) cells agglutination, transepithelial electrical resistance of T84-cell monolayers,

360   intracellular levels of TG2 and phosphorylated form of protein 42–44 in human

361   leukemic K562(S) and human colon adenocarcinoma T84 cell lines. No reaction was

362   observed from the other 2 cultivars (115).

363

364   *3.5 Study quality*

365

366   Among the 23 RCTs, the majority had some concerns (n=17, 73.9%) mostly in domains

367   of randomization and five studies were judged as having high risk of bias. The majority

368   of non-randomized trials were of moderate quality (n=20, 95.2%) with only a single trial

369   being classified as low risk of bias. The eight observational studies seven were judged

370   as moderate quality. Among 32 *in vitro* studies, the majority of studies (n=27, 84.4%)

371   were judged as reliable without restrictions, while only five studies are reliable with

372   restrictions (**Supplemental Tables 8-12**).

373

374   **4. DISCUSSION**

375

376   In this systematic review, the effects of oats on GI health in humans were reviewed

377   and the study population included healthy adults, adults with certain conditions (i.e.

378   UC, CeD, elevated cholesterol, obesity) and pediatric population (i.e. healthy and with

379   CeD). Oats are able to influence the GI microbial communities that supports the

380   proliferation of *Lactobacillus* and *Bifidobacterium* in most studies. There were

381   increased levels of SCFAs, increased branch chain fatty acids and decreased of

382   proteolytic enzymes. Clinically, those consuming oats had no significant improvement

383   in quality of life and the majority of studies showed no changes in GI symptoms with

384   oat consumption, whereas, a few studies reported an increase in diarrhea and

385   constipation or showed increasing GSRS scores in individuals exposed to oats. In

386   pediatric and adults with CeD, moderate consumption of oats is generally tolerated and

387   allows mucosal recovery even in the long-term. Larger amounts of oats are able to add

388   dietary variety and nutritional benefits to CeD patients, however, they may increase

389   the frequency of adverse bowel symptoms. Adding enzymatic activity by fermenting

390   oats or preserving internal enzymes by not kilning may reduce negative symptoms

391   (79). A subset of individuals with CeD may be sensitive to oats wherein there are

392   increased IELs in the intestinal mucosa but a normal histologic villus structure is

393   maintained.

394

395   Our findings on increased count of *Lactobacillus spp*. and *Bifidobacterium spp*. with

396   oat consumption could be explained by the nutrient content of the oat and its

397   metabolism. Oat is a rich source of dietary fibers including β-glucans, polysaccharides

398   that are known to modulate gut microbial community (116). They are considered

399   prebiotic, non-digestible food ingredients that are fermented by the intestinal microflora

400   and may selectively regulate the growth of a group or groups of bacteria in the colon

401   that can improve health (117, 118). *Bifidobacterium* and *Lactobacillus* are commonly

402   targeted microorganisms in the gut for their associated health benefits. *Bifidobacterium*

403   has been shown to be protective in diseases such as colorectal cancer, diarrhea,

404   necrotizing entercolitis, inflammatory bowel disease and known to competitively inhibit

405   pathogens to binding sites in the epithelial cells (119, 120). *Lactobacillus*, on the other

406   hand, has protective effects on the intestinal permeability induced by inflammation,

407   chemicals and stress and serves as an important source of lactate that is further

408   metabolized to SCFAs (121). Bacterial fermentation of dietary fibers in the colon

409   generally produces SCFAs such as acetate, propionate and butyrate. *Bifidobacterium*

410   are able to produce acetate (122) and thus contribute to the SCFAs in the gut.

411   Likewise, *Bifidobacterium* allows the co-inhabitation with butyrate producing bacteria

412   and butyrate is significantly enriched with consumption of dietary fibers (123). The most

413 dominantly represented butyrate producing bacterial genera are *Faecalbacterium,*

414 *Roseburia, Anaerostipes* and *Eubacterium* (120). Benefits from the consumption of

415 oats could be attributed to their effects on the gut microbial community especially

416 targeting known bacterial groups that promote GI health benefits.

417

418 Consumption of oats has encountered barriers among individuals with CeD despite the

419 advantage of providing better nutrient content compared to a regular GFD. Strict

420 consumption of GFD is the main clinical management strategy in preventing

421 development of debilitating symptoms and mucosal inflammation among individuals

422 with CeD. On the other hand, the evidence suggests that the CeD patients' diet

423 generally reproduce, despite minor differences, the eating behavior of the general

424 population, suggesting that these individuals may not follow dietary recommendations

425 strictly (124). In the current review, consumption of oats is generally tolerated among

426 pediatric populations and adults with CeD even up to five years. This corroborates

427 previously published data which shows that oats can be tolerated with no significant

428 changes in clinical symptoms (3, 21-23) but there might be histologic, serologic and

429 immunologic manifestation pointing to an inflammatory reaction at the intestinal

430 mucosa without manifestation of the disease (77, 99). Oat sensitive individuals may

431 experience an increase in diarrhea frequency as consequence of the inflammatory

432 reaction of the gut mucosa to the oat. It may be that oat processing (such as kilning,

433 fermentation, gluten-free cleaning) and cultivar selection may be important factors to

434 determine on whether oat induces a positive or negative health response.

435

436 *In vitro* and clinical studies in this review suggest that individuals with CeD may have

437 villus structure that does not significantly differ in the histomorphology score for normal

438 duodenal mucosa but there is an increase in IELs and upregulated inflammatory

439   mediators (80, 106, 111). This could explain the increased diarrhea in patients but

440   without the other associated symptoms for a full-blown disease. Inflamed cells of the

441   villous structure in the duodenum especially the apical cells can lead to malabsorption

442   of carbohydrates and solutes leading to water retention and thus the diarrhea.

443   Sensitivity to oats has been seen in few individuals and deemed insignificant (21)

444   though Haboubi et al. (22) argues that the withdrawals from the clinical trials might

445   represent this group and more effort to follow up should have been conducted.

446

447   *4.1 Strengths and limitations of current review*

448

449   The review was guided by published guidelines and the best available tools to appraise

450   the quality of the evidence. To our knowledge, this is the first report that includes a

451   comprehensive set of parameters of microbial changes, GI symptoms, histological and

452   immunological markers in the gut. In order to identify as many relevant studies as

453   possible and reduce the risk of publication bias, a sensitive search strategy was used

454   and additional resources were searched including the reference lists of included trials

455   and relevant systematic reviews. However, we were not able to search all existing

456   online databases. No restrictions on language were used but we may have missed

457   articles published in languages other than English. Due to high heterogeneity of

458   interventions and study designs, we were not able to provide a quantitative synthesis.

459   We were able to provide an illustrative summary of the most important findings (**Figure

460   2**) and provided a summary table (**Table 2**) to simplify the interpretation of the findings.

461   In addition, we acknowledge that our findings were based on not only RCTs but also

462   observational and non-RCT data. Finally, we did not identify any study focusing on IBS

463   and found 3 on IBD therefore we focused the review to individuals with CeD and

464   individuals without GI symptoms.

465

466   This review shows that oat consumption has multiple benefits. The grain influences the

467   gut microbiota but studies included in the review are limited in scope of investigating

468   the microbiome. The studies focused and targeted established bacterial genera that

469   might have led to other beneficial bacteria being missed. Some of the studies reported

470   various taxa with the genera being the most commonly used. Improvement in microbial

471   identification with next generation sequencing could lead to improved characterization

472   of beneficial microorganisms, inter-relationships and networks of bacteria. Moreover,

473   metabolites investigated in the studies are limited to SCFAs and have not included

474   metabolites from protein and fat degradation despite being included in the search

475   strategy. Moreover, different oat cultivars showed different effects on GI parameters *in*

476   *vitro* adding another possible level of complexity with some varieties possibly offering

477   health benefits while others the opposite.

478

479   *4.2 Conclusions*

480

481   The clinical studies on the association between oat intake with respect to

482   gastrointestinal health remain to be few and prone to risk of bias. Studies were

483   conducted in a few countries and some trials were characterized by significant

484   participant drop-out. We have included non-randomized controlled trials but most have

485   moderate quality owing to the lack of control groups and reliance to a before-after

486   intervention design. Oat was shown to influence the GI microbial community with no

487   significant differences in GI symptoms to those not taking oats. Oat was generally well

488   tolerated among pediatric population and adults with CeD. The *in vitro* studies provide

489   molecular insights to some controversies especially on oat sensitive individuals and

490   their gut mucosa. However, it remains unknown how prevalent oat sensitive individuals

491   are especially among individuals with CeD and other inflammatory bowel diseases.

492   Further studies are needed to improve clinical management and increase the inclusion

493   of oats in the gluten-free diets.

494

495   **Author Contributions**

496   Study concept and design: MG and HK; Search strategy creation and online database

497   search: BMinder; Acquisition, collection, interpretation of data: EV, JS, AB, AHG, RZ,

498   JLF, SS, BMetzger, WB, TM, MG, HK; Drafting of the manuscript: EV, JS, MG, HK;

499   Critical revision of the manuscript for important intellectual content: EV, JS, AB, AHG,

500   BMinde, RZ, JLF, SS, BMetzger, WB, TM, MG, HK. Study supervision: MG and HK;

501   All authors approved the final version of the manuscript.

502

503

References

1.   Raguindin PF, Itodo OA, Stoyanov J, Dejanovic GM, Gamba M, Asllanaj E, Minder B, Bussler W, Metzger B, Muka T, et al. A systematic review of phytochemicals in oat and buckwheat. Food Chem 2021;338.
2.   Chang HC, Huang CN, Yeh DM, Wang SJ, Peng CH, Wang CJ. Oat prevents obesity and abdominal fat distribution, and improves liver function in humans. Plant Foods Hum Nutr. 2013;68:18-23.
3.   Thies F, Masson LF, Boffetta P, Kris-Etherton P. Oats and bowel disease: A systematic literature review. Br J Nutr. 2014;112 Suppl 2:S31-43.
4.   Tapola N, Karvonen H, Niskanen L, Mikola M, Sarkkinen E. Glycemic responses of oat bran products in type 2 diabetic patients. Nutr Metab Cardiovasc Dis. 2005;15:255-61.
5.   Korczak R, Kocher M, Swanson KS. Effects of oats on gastrointestinal health as assessed by in vitro, animal, and human studies. Nutr Rev. 2020;78:343-63.
6.   Mälkki Y, Virtanen E. Gastrointestinal effects of oat bran and oat gum: A review. Lebensm Wiss Technol. 2001;34:337-47.
7.   Rose DJ. Impact of whole grains on the gut microbiota: The next frontier for oats? Br J Nutr. 2014;112:S44-9.
8.   Nouvenne A, Ticinesi A, Tana C, Prati B, Catania P, Miraglia C, De' Angelis GL, Di Mario F, Meschi T. Digestive disorders and intestinal microbiota. Acta Biomed. 2018;89:47-51.
9.   Altajar S, Moss A. Inflammatory bowel disease environmental risk factors: Diet and gut microbiota. Curr Gastroenterol Rep. 2020;22:57.
10.   Hanus M, Parada-Venegas D, Landskron G, Wielandt AM, Hurtado C, Alvarez K, Hermoso MA, Lopez-Kostner F, De la Fuente M. Immune system, microbiota, and microbial metabolites: The unresolved triad in colorectal cancer microenvironment. Front Immunol. 2021;12:612826.
11.   Mari A, Abu Baker F, Mahamid M, Sbeit W, Khoury T. The evolving role of gut microbiota in the management of irritable bowel syndrome: An overview of the current knowledge. J Clin Med. 2020;9:685.
12.   Valitutti F, Cucchiara S, Fasano A. Celiac disease and the microbiome. Nutrients. 2019;11:2403.
13.   Dominianni C, Sinha R, Goedert JJ, Pei Z, Yang L, Hayes RB, Ahn J. Sex, body mass index, and dietary fiber intake influence the human gut microbiome. PLoS One. 2015;10:e0124599.
14.   Sanna S, van Zuydam NR, Mahajan A, Kurilshikov A, Vich Vila A, Vosa U, Mujagic Z, Masclee AAM, Jonkers D, Oosting M, et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. Nat Genet. 2019;51:600-5.
15.   Tian Y, Xu Q, Sun L, Ye Y, Ji G. Short-chain fatty acids administration is protective in colitis-associated colorectal cancer development. J Nutr Biochem. 2018;57:103-9.
16.   Parada Venegas D, De la Fuente MK, Landskron G, Gonzalez MJ, Quera R, Dijkstra G, Harmsen HJM, Faber KN, Hermoso MA. Short chain fatty acids (scfas)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol. 2019;10:277.
17.   Liu H, Wang J, He T, Becker S, Zhang G, Li D, Ma X. Butyrate: A double-edged sword for health? Adv Nutr. 2018;9:21-9.
18.   Canani RB, Costanzo MD, Leone L, Pedata M, Meli R, Calignano A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World J Gastroenterol. 2011;17:1519-28.
19.   Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. Gut Microbes. 2016;7:189-200.
20.   Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, et al. Prebiotic effects: Metabolic and health benefits. Br J Nutr. 2010;104:S1-63.
21.   Garsed K, Scott BB. Can oats be taken in a gluten-free diet? A systematic review. Scand J Gastroenterol. 2007;42:171-8.
22.   Haboubi NY, Taylor S, Jones S. Coeliac disease and oats: A systematic review. Postgrad Med J. 2006;82:672-8.
23.   Pinto-Sánchez MI, Causada-Calo N, Bercik P, Ford AC, Murray JA, Armstrong D, Semrad C, Kupfer SS, Alaedini A, Moayyedi P, et al. Safety of adding oats to a gluten-free diet for patients with celiac disease: Systematic review and meta-analysis of clinical and observational studies. Gastroenterology. 2017;153:395-409.
24.   Muka T, Glisic M, Milic J, Verhoog S, Bohlius J, Bramer W, Chowdhury R, Franco OH. A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research. Eur J Epidemiol. 2020;35:49-60.

25.	Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. PLoS Med. 2009;6:e1000097.
26.	Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, et al. Rob 2: A revised tool for assessing risk of bias in randomised trials. BMJ 2019;366.
27.	NIH National Heart Lung and Blood Institute. Qualty assessment of controlled intervention studies. 2014 [cited 2020 27 Feb]; Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
28.	NIH National Heart Lung and Blood Institute. Quality assessment tool for before-after (pre-post) studies with no control group. 2014 [cited 2020 27 Feb]; Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
29.	Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The newcastle-ottawa scale (nos) for assessing the quality of nonrandomised studies in meta-analyses. 2013 [cited 2020 27 Feb]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
30.	Schneider K, Schwarz M, Burkholder I, Kopp-Schneider A, Edler L, Kinsner-Ovaskainen A, Hartung T, Hoffmann S. "Toxrtool", a new tool to assess the reliability of toxicological data. Toxicol Lett. 2009;189:138-44.
31.	Mårtensson O, Biörklund M, Lambo AM, Dueñas-Chasco M, Irastorza A, Holst O, Norin E, Welling G, Öste R, Önning G. Fermented, ropy, oat-based products reduce cholesterol levels and stimulate the bifidobacteria flora in humans. Nutr Res. 2005;25:429-42.
32.	Connolly ML, Tzounis X, Tuohy KM, Lovegrove JA. Hypocholesterolemic and prebiotic effects of a whole-grain oat-based granola breakfast cereal in a cardio-metabolic "at risk" population. Front Microbiol. 2016;7:1675.
33.	Johansson ML, Nobaek S, Berggren A, Nyman M, Björck I, Ahrné S, Jeppsson B, Molin G. Survival of lactobacillus plantarum dsm 9843 (299v), and effect on the short-chain fatty acid content of faeces after ingestion of a rose-hip drink with fermented oats. Int J Food Microbiol. 1998;42:29-38.
34.	Berggren A, Söderberg L, Önning G, Hagslätt MLJ, Axelsson I. Intestinal function, microflora and nutrient intake of children after administration of a fermented oat product containing lactobacillus plantarum dsm 9843 (299v). Microb Ecol Health Dis. 2003;15:160-8.
35.	Duysburgh C, Van den Abbeele P, Kamil A, Fleige L, De Chavez PJ, Chu Y, Barton W, O'Sullivan O, Cotter PD, Quilter K, et al. In vitro-in vivo validation of stimulatory effect of oat ingredients on lactobacilli. Pathogens. 2021;10:235.
36.	Pino JL, Mujica V, Arredondo M. Effect of dietary supplementation with oat beta-glucan for 3 months in subjects with type 2 diabetes: A randomized, double-blind, controlled clinical trial. J Funct Food. 2021;77:104311.
37.	Ye M, Sun J, Chen Y, Ren Q, Li Z, Zhao Y, Pan Y, Xue H. Oatmeal induced gut microbiota alteration and its relationship with improved lipid profiles: A secondary analysis of a randomized clinical trial. Nutr Metab (Lond). 2020;17:85.
38.	Tjellström B, Stenhammar L, Sundqvist T, Fälth-Magnusson K, Hollén E, Magnusson KE, Norin E, Midtvedt T, Högberg L. The effects of oats on the function of gut microflora in children with coeliac disease. Aliment Pharmacol Therapeut. 2014;39:1156-60.
39.	Nyman M, Nguyen TD, Wikman O, Hjortswang H, Hallert C. Oat bran increased fecal butyrate and prevented gastrointestinal symptoms in patients with quiescent ulcerative colitis-randomized controlled trial. Crohn's and Colitis 360. 2020;2:1-13.
40.	Nilsson U, Johansson M, Nilsson A, Bjorck I, Nyman M. Dietary supplementation with beta-glucan enriched oat bran increases faecal concentration of carboxylic acids in healthy subjects. Eur J Clin Nutr. 2008;62:978-84.
41.	Valeur J, Puaschitz NG, Midtvedt T, Berstad A. Oatmeal porridge: Impact on microflora-associated characteristics in healthy subjects. Br J Nutr. 2016;115:62-7.
42.	Hallert C, Björck I, Nyman M, Pousette A, Grännö C, Svensson H. Increasing fecal butyrate in ulcerative colitis patients by diet: Controlled pilot study. Inflamm Bowel Dis. 2003;9:116-21.
43.	Li M, Koecher K, Hansen L, Ferruzzi MG. Phenolics from whole grain oat products as modifiers of starch digestion and intestinal glucose transport. J Agr Food Chem. 2017;65:6831-9.
44.	Van den Abbeele P, Kamil A, Fleige L, Chung Y, De Chavez P, Marzorati M. Different oat ingredients stimulate specific microbial metabolites in the gut microbiome of three human individuals in vitro. ACS Omega. 2018;3:12446-56.
45.	Kristek A, Wiese M, Heuer P, Kosik O, Schär MY, Soycan G, Alsharif S, Kuhnle GGC, Walton G, Spencer JPE. Oat bran, but not its isolated bioactive β-glucans or polyphenols, have a bifidogenic effect in an in vitro fermentation model of the gut microbiota. Br J Nutr. 2019;121:549-59.
46.	Connolly ML, Lovegrove JA, Tuohy KM. In vitro evaluation of the microbiota modulation abilities of different sized whole oat grain flakes. Anaerobe. 2010;16:483-8.

47.   Connolly ML, Lovegrove JA, Tuohy KM. In vitro fermentation characteristics of whole grain wheat flakes and the effect of toasting on prebiotic potential. J Med Food. 2012;15:33-43.

48.   Kim HJ, White PJ. In vitro fermentation of oat flours from typical and high β-glucan oat lines. J Agr Food Chem. 2009;57:7529-36.

49.   Tsitko I, Wiik-Miettinen F, Mattila O, Rosa-Sibakov N, Seppanen-Laakso T, Maukonen J, Nordlund E, Saarela M. A small in vitro fermentation model for screening the gut microbiota effects of different fiber preparations. Int J Mol Sci. 2019;20:1925.

50.   Hernot DC, Boileau TW, Bauer LL, Swanson KS, Fahey Jr GC. In vitro digestion characteristics of unprocessed and processed whole grains and their components. J Agr Food Chem. 2008;56:10721-6.

51.   Wood PJ, Arrigoni E, Miller SS, Amado R. Fermentability of oat and wheat fractions enriched in beta-glucan using human fecal inoculation. Cereal Chem. 2002;79:445-54.

52.   Kedia G, Vazquez JA, Charalampopoulos D, Pandiella SS. In vitro fermentation of oat bran obtained by debranning with a mixed culture of human fecal bacteria. Curr Microbiol. 2009;58:338-42.

53.   Yang J, Keshavarzian A, Rose DJ. Impact of dietary fiber fermentation from cereal grains on metabolite production by the fecal microbiota from normal weight and obese individuals. J Med Food. 2013;16:862-7.

54.   Slade AP, Wyatt GM, Bayliss CE, Waites WM. Comparison of populations of human faecal bacteria before and after in vitro incubation with plant cell wall substrates. J Appl Microbiol. 1987;62:231-40.

55.   Akkerman R, Logtenberg MJ, An R, Van Den Berg MA, de Haan BJ, Faas MM, Zoetendal E, de Vos P, Schols HA. Endo-1,3(4)-beta-glucanase-treatment of oat beta-glucan enhances fermentability by infant fecal microbiota, stimulates dectin-1 activation and attenuates inflammatory responses in immature dendritic cells. Nutrients. 2020;12:1660.

56.   Wang P, Zhang S, Yerke A, Ohland CL, Gharaibeh RZ, Fouladi F, Fodor AA, Jobin C, Sang S. Avenanthramide metabotype from whole-grain oat intake is influenced by faecalibacterium prausnitzii in healthy adults. J Nutr. 2021;151:1426-35.

57.   Queenan KM, Stewart ML, Smith KN, Thomas W, Fulcher RG, Slavin JL. Concentrated oat β-glucan, a fermentable fiber, lowers serum cholesterol in hypercholesterolemic adults in a randomized controlled trial. Nutr J. 2007;6:1-8.

58.   Hughes SA, Shewry PR, Gibson GR, McCleary BV, Rastall RA. In vitro fermentation of oat and barley derived β-glucans by human faecal microbiota. FEMS Microbiol Ecol. 2008;64:482-93.

59.   Gamage HKAH, Tetu SG, Chong RWW, Ashton J, Packer NH, Paulsen IT. Cereal products derived from wheat, sorghum, rice and oats alter the infant gut microbiota in vitro. Sci Rep. 2017;7:1-12.

60.   Brahma S, Weier SA, Rose DJ. Moisture content during extrusion of oats impacts the initial fermentation metabolites and probiotic bacteria during extended fermentation by human fecal microbiota. Food Res Int. 2017;97:209-14.

61.   Titgemeyer EC, Bourquin LD, Fahey Jr GC, Garleb KA. Fermentability of various fiber sources by human fecal bacteria in vitro. Am J Clin Nutr. 1991;53:1418-24.

62.   Roye C, Bulckaen K, De Bondt Y, Liberloo I, Van De Walle D, Dewettinck K, Courtin CM. Side-by-side comparison of composition and structural properties of wheat, rye, oat, and maize bran and their impact on in vitro fermentability. Cereal Chem. 2020;97:20-33.

63.   Nordlund E, Aura AM, Mattila I, Kössö T, Rouau X, Poutanen K. Formation of phenolic microbial metabolites and short-chain fatty acids from rye, wheat, and oat bran and their fractions in the metabolical in vitro colon model. J Agric Food Chem. 2012;60:8134-45.

64.   Lebet V, Arrigoni E, Amado R. Measurement of fermentation products and substrate disappearance during incubation of dietary fibre sources with human faecal flora. Lebensm Wiss Technol. 1998;31:473-9.

65.   Pham VT, Seifert N, Richard N, Raederstorff D, Steinert R, Prudence K, Hasan Mohajeri M. The effects of fermentation products of prebiotic fibres on gut barrier and immune functions in vitro. PeerJ. 2018:e5288.

66.   Dong JL, Yang M, Zhu YY, Shen RL, Zhang KY. Comparative study of thermal processing on the physicochemical properties and prebiotic effects of the oat β-glucan by in vitro human fecal microbiota fermentation. Food Res Int. 2020;138:109818.

67.   Glei M, Zetzmann S, Lorkowski S, Dawczynski C, Schlormann W. Chemopreventive effects of raw and roasted oat flakes after in vitro fermentation with human faecal microbiota. Int J Food Sci Nutr. 2021;72:57-69.

68.   Keenan JM, Wenz JB, Myers S, Ripsin C, Huang Z. Randomized, controlled, crossover trial of oat bran in hypercholesterolemic subjects. J Fam Pract. 1991;33:600-8.

69.   Cicero AFG, Fogacci F, Veronesi M, Strocchi E, Grandi E, Rizzoli E, Poli A, Marangoni F, Borghi C. A randomized placebo-controlled clinical trial to evaluate the medium-term effects of oat fibers on human health: The beta-glucan effects on lipid profile, glycemia and intestinal health (belt) study. Nutrients. 2020;12:686.

70.   Hakkola S, Nylund L, Rosa-Sibakov N, Yang B, Nordlund E, Pahikkala T, Kalliomaki M, Aura AM, Linderborg KM. Effect of oat beta-glucan of different molecular weights on fecal bile acids, urine metabolites and pressure in the digestive tract - a human cross over trial. Food Chem. 2021;342:128219.

71.   Pitkälä KH, Strandberg TE, Finne-Soveri UH, Ouwehand AC, Poussa T, Salminen S. Fermented cereal with specific bifidobacteria normalizes bowel movements in elderly nursing home residents. A randomized, controlled trial. J Nutr Health Aging. 2007;11:305-11.

72.   Sturtzel B, Elmadfa I. Intervention with dietary fiber to treat constipation and reduce laxative use in residents of nursing homes. Ann Nutr Metabol. 2008;52:54-6.

73.   Valle-Jones JC. An open study of oat bran meal biscuits ('lejfibre') in the treatment of constipation in the elderly. Curr Med Res Opin. 1985;9:716-20.

74.   Paruzynski H, Korczak R, Wang Q, Slavin J. A pilot and feasibility study of oatmeal consumption in children to assess markers of bowel function. J Med Food. 2019;23:554-9.

75.   Kajs TM, Fitzgerald JA, Buckner RY, Coyle GA, Stinson BS, Morel JG, Levitt MD. Influence of a methanogenic flora on the breath h2 and symptom response to ingestion of sorbitol or oat fiber. Am J Gastroenterol. 1997;92:89-94.

76.   Svelund J, Sjodin I, Doteval G. Gsrs--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988;33:129-34.

77.   Peraaho M, Kaukinen K, Mustalahti K, Vuolteenaho N, Maki M, Laippala P, Collin P. Effect of an oats-containing gluten-free diet on symptoms and quality of life in coeliac disease. A randomized study. Scand J Gastroenterol. 2004;39:27-31.

78.   Lionetti E, Gatti S, Galeazzi T, Caporelli N, Francavilla R, Cucchiara S, Roggero P, Malamisura B, Iacono G, Tomarchio S, et al. Safety of oats in children with celiac disease: A double-blind, randomized, placebo-controlled trial. J Pediatr. 2018;194:116-22

79.   Kemppainen TA, Heikkinen MT, Ristikankare MK, Kosma VM, Sontag-Strohm TS, Brinck O, Salovaara HO, Julkunen RJ. Unkilned and large amounts of oats in the coeliac disease diet: A randomized, controlled study. Scand J Gastroenterol. 2008;43:1094-101.

80.   Hoffenberg EJ, Haas J, Drescher A, Barnhurst R, Osberg I, Bao F, Eisenbarth G. A trial of oats in children with newly diagnosed celiac disease. J Pediatr. 2000;137:361-6.

81.   Størsrud S, Olsson M, Arvidsson Lenner R, Nilsson LÅ, Nilsson O, Kilander A. Adult coeliac patients do tolerate large amounts of oats. Eur J Clin Nutr. 2003;57:163-9.

82.   Størsrud S, Hulthén LR, Lenner RA. Beneficial effects of oats in the gluten-free diet of adults with special reference to nutrient status, symptoms and subjective experiences. Br J Nutr. 2003;90:101-7.

83.   Sey MSL, Parfitt J, Gregor J. Prospective study of clinical and histological safety of pure and uncontaminated canadian oats in the management of celiac disease. JPEN J Parenter Enteral Nutr. 2011;35:459-64.

84.   Baker PG, Read AE. Oats and barley toxicity in coeliac patients. Postgrad Med J. 1976;52:264-8.

85.   Lundin KEA, Nilsen EM, Scott HG, Løberg EM, Gjøen A, Bratlie J, Skar V, Mendez E, Loøvik A, Kett K. Oats induced villous atrophy in coeliac disease. Gut. 2003;52:1649-52.

86.   Tuire I, Marja-Leena L, Teea S, Katri H, Jukka P, Päivi S, Heini H, Markku M, Pekka C, Katri K. Persistent duodenal intraepithelial lymphocytosis despite a long-term strict gluten-free diet in celiac disease. Am J Gastroenterol. 2012;107:1563-9.

87.   Tapsas D, Fälth-Magnusson K, Högberg L, Hammersjö JT, Hollén E. Swedish children with celiac disease comply well with a gluten-free diet, and most include oats without reporting any adverse effects: A long-term follow-up study. Nutr Res. 2014;34:436-41.

88.   Janatuinen EK, Kemppainen TA, Julkunen RJK, Kosma VM, Mäki M, Heikkinen M, Uusitupa MIJ. No harm from five year ingestion of oats in coeliac disease. Gut. 2002;50:332-5.

89.   Aaltonen K, Laurikka P, Huhtala H, Maki M, Kaukinen K, Kurppa K. The long-term consumption of oats in celiac disease patients is safe: A large cross-sectional study. Nutrients. 2017;9:611.

90.   Nylund L, Hakkola S, Lahti L, Salminen S, Kalliomaki M, Yang B, Linderborg KM. Diet, perceived intestinal well-being and compositions of fecal microbiota and short chain fatty acids in oat-using subjects with celiac disease or gluten sensitivity. Nutrients. 2020;12:2570.

91.   Kaukinen K, Collin P, Huhtala H, Maki M. Long-term consumption of oats in adult celiac disease patients. Nutrients. 2013;5:4380-9.

92.   Van Kruiningen HJ, Joossens M, Vermeire S, Joossens S, Debeugny S, Gower-Rousseau C, Cortot A, Colombel JF, Rutgeerts P, Vlietinck R. Environmental factors in familial crohn's disease in belgium. Inflamm Bowel Dis. 2005;11:360-5.

93.   Janatuinen EK, Pikkarainen PH, Kemppainen TA, Kosma VM, Järvinen RMK, Uusitupa MIJ, Julkunen RJK. A comparison of diets with and without oats in adults with celiac disease. New Engl J Med. 1995;333:1033-7.

94.   Janatuinen EK, Kemppainen TA, Pikkarainen PH, Holm KH, Kosma VM, Uusitupa MIJ, Mäki M, Julkunen RJK. Lack of cellular and humoral immunological responses to oats in adults with coeliac disease. Gut. 2000;46:327-31.

95.   Högberg L, Laurin P, Fâlth-Magnusson K, Grant C, Grodzinsky E, Jansson G, Ascher H, Browaldh L, Hammersjö JÅ, Lindberg E, et al. Oats to children with newly diagnosed coeliac disease: A randomised double blind study. Gut. 2004;53:649-54.

96.   Holm K, Maki M, Vuolteenaho N, Mustalahti K, Ashorn M, Ruuska T, Kaukinen K. Oats in the treatment of childhood coeliac disease: A 2-year controlled trial and a long-term clinical follow-up study. Aliment Pharmacol Ther. 2006;23:1463-72.

97.   Koskinen O, Villanen M, Korponay-Szabo I, Lindfors K, Mäki M, Kaukinen K. Oats do not induce systemic or mucosal autoantibody response in children with coeliac disease. J Pediatr Gastroenterol Nutr. 2009;48:559-65.

98.   Hollen E, Holmgren Peterson K, Sundqvist T, Grodzinsky E, Hogberg L, Laurin P, Stenhammar L, Falth-Magnusson K, Magnusson KE. Coeliac children on a gluten-free diet with or without oats display equal anti-avenin antibody titres. Scand J Gastroenterol. 2006;41:42-7.

99.   Sjöberg V, Hollén E, Pietz G, Magnusson KE, Fälth-Magnusson K, Sundström M, Peterson KH, Sandstrom O, Hernell O, Hammarström S, et al. Noncontaminated dietary oats may hamper normalization of the intestinal immune status in childhood celiac disease. Clin Transl Gastroenterol. 2014;5:e58.

100.   Dissanayake AS, Truelove SC, Whitehead R. Lack of harmful effect of oats on small intestinal mucosa in coeliac disease. Br Med J. 1974;4:189-91.

101.   Srinivasan U, Leonard N, Jones E, Kasarda DD, Weir DG, O'Farrelly C, Feighery C. Absence of oats toxicity in adult coeliac disease. Br Med J. 1996;313:1300-1.

102.   Srinivasan U, Jones E, Weir DG, Feighery C. Lactase enzyme, detected immunohistochemically, is lost in active celiac disease, but unaffected by oats challenge. Am J Gastroenterol. 1999;94:2936-41.

103.   Cooper SEJ, Kennedy NP, Mohamed BM, Abuzakouk M, Dunne J, Byrne G, McDonald G, Davies A, Edwards C, Kelly J, et al. Immunological indicators of coeliac disease activity are not altered by long-term oats challenge. Clin Exp Immunol. 2013;171:313-8.

104.   Srinivasan U, Jones E, Carolan J, Feighery C. Immunohistochemical analysis of coeliac mucosa following ingestion of oats. Clin Exp Immunol. 2006;144:197-203.

105.   Kemppainen T, Janatuinen E, Holm K, Kosma VM, Heikkinen M, Maki M, Laurila K, Uusitupa M, Julkunen R. No observed local immunological response at cell level after five years of oats in adult coeliac disease. Scand J Gastroenterol. 2007;42:54-9.

106.   Hardy MY, Tye-Din JA, Stewart JA, Schmitz F, Dudek NL, Hanchapola I, Purcell AW, Anderson RP. Ingestion of oats and barley in patients with celiac disease mobilizescross-reactive t cells activated by avenin peptides andimmuno-dominant hordein peptides. J Autoimmun. 2015;56:56-65.

107.   Emanuél V, Vokhmianina NV, Gavriliuk IP, Krasil'nikov VN, Alpat'eva NV. Value of serological diagnosis of celiac disease for the determination of intolerance to prolamines of certain varieties of oats in patients with celiac disease. Klin Lab Diagn. 2007:32-4.

108.   Picarelli A, Di Tola M, Sabbatella L, Gabrielli F, Di Cello T, Anania MC, Mastracchio A, Silano M, De Vincenzi M. Immunologic evidence of no harmful effect of oats in celiac disease. Am J Clin Nutr. 2001;74:137-40.

109.   Kilmartin C, Lynch S, Abuzakouk M, Wieser H, Feighery C. Avenin fails to induce a th1 response in coeliac tissue following in vitro culture. Gut. 2003;52:47-52.

110.   Hollen E, Hogberg L, Stenhammar L, Falth-Magnusson K, Magnusson KE. Antibodies to oat prolamines (avenins) in children with coeliac disease. Scand J Gastroenterol. 2003;38:742-6.

111.   Arentz-Hansen H, Fleckenstein B, Molberg Ø, Scott H, Koning F, Jung G, Roepstorff P, Lundin KEA, Sollid LM. The molecular basis for oat intolerance in patients with celiac disease. PLoS Med. 2004;1:e1.

112.   Kilmartin C, Wieser H, Abuzakouk M, Kelly J, Jackson J, Feighery C. Intestinal t cell responses to cereal proteins in celiac disease. Dig Dis Sci. 2006;51:202-9.

113.   Maglio M, Mazzarella G, Barone MV, Gianfrani C, Pogna N, Gazza L, Stefanile R, Camarca A, Colicchio B, Nanayakkara M, et al. Immunogenicity of two oat varieties, in relation to their safety for celiac patients. Scand J Gastroenterol. 2011;46:1194-205.

114.   Comino I, Real A, De Lorenzo L, Cornell H, López-Casado MÁ, Barro F, Lorite P, Torres MI, Cebolla Á, Sousa C. Diversity in oat potential immunogenicity: Basis for the selection of oat varieties with no toxicity in coeliac disease. Gut. 2011;60:915-22.

115.   Silano M, Penas Pozo E, Uberti F, Manferdelli S, Del Pinto T, Felli C, Budelli A, Vincentini O, Restani P. Diversity of oat varieties in eliciting the early inflammatory events in celiac disease. Eur J Clin Nutr. 2014;53:1177-86.

116.   Jayachandran M, Chen J, Chung SSM, Xu B. A critical review on the impacts of beta-glucans on gut microbiota and human health. J Nutr Biochem. 2018;61:101-10.

117.   Gibson GR, Probert HM, Loo JV, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. Nutr Res Rev. 2007;17:259-75.

118.   Tosh SM, Bordenave N. Emerging science on benefits of whole grain oat and barley and their soluble dietary fibers for heart health, glycemic response, and gut microbiota. Nutr Rev. 2020;78:13-20.

119.   O'Callaghan A, van Sinderen D. Bifidobacteria and their role as members of the human gut microbiota. Front Microbiol. 2016;7:925.

120.   Riviere A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and butyrate-producing colon bacteria: Importance and strategies for their stimulation in the human gut. Front Microbiol. 2016;7:979.

121.   Ahrne S, Hagslatt ML. Effect of lactobacilli on paracellular permeability in the gut. Nutrients. 2011;3:104-17.

122.   Fukuda S, Toh H, Hase K, Oshima K, Nakanishi Y, Yoshimura K, Tobe T, Clarke JM, Topping DL, Suzuki T, et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate. Nature. 2011;469:543-7.

123.   So D, Whelan K, Rossi M, Morrison M, Holtmann G, Kelly JT, Shanahan ER, Staudacher HM, Campbell KL. Dietary fiber intervention on gut microbiota composition in healthy adults: A systematic review and meta-analysis. Am J Clin Nutr. 2018;107:965-83.

124.   Valitutti F, Iorfida D, Anania C, Trovato CM, Montuori M, Cucchiara S, Catassi C. Cereal consumption among subjects with celiac disease: A snapshot for nutritional considerations. Nutrients. 2017;9:396.

Table 1. Summary of the included studies in the systematic review of oat intake and its effect in GI health in individuals with and without GI disease.

Lead Author, Publication Year	Study Design	Population Characteristic	Risk of Bias[1]	Summarized Finding
Oat intake and changes in gut microbiome				
Connolly, 2016(32)	RCT	Adults with glucose intolerance or elevated cholesterol	Some Concern	Table 2; Supplemental Table 1
Johansson, 1998(33)	RCT	Healthy adults	Some Concern	Table 2; Supplemental Table 1
Berggren, 2008(34)	RCT	Healthy pediatric population	Some Concern	Table 2; Supplemental Table 1
Martenson, 2005(31)	RCT	Healthy adults	Some Concern	Table 2; Supplemental Table 1
Duysburgh, 2021(35)	RCT	Adults with elevated cholesterol	Some Concern	Table 2; Supplemental Table 1
Ye, 2020(37)	RCT	Adults with elevated cholesterol	Some Concern	Table 2; Supplemental Table 1
Pino, 2020(36)	RCT	Adults with type 2 diabetes	Some Concern	Table 2; Supplemental Table 1
Tjellstrom, 2014 (38)	RCT	Pediatric population with CeD	Some Concern	Table 2; Supplemental Table 3
Nyman, 2020(39)	RCT	Adults with UC	Some Concern	Table 2; Supplemental Table 3
Nilsson, 2008(40)	Non-randomized trial	Healthy adults	Moderate	Table 2;Supplemental Table 2
Valeur, 2015(41)	Non-randomized trial	Healthy adults	Moderate	Table 2;Supplemental Table 2
Li, 2017(43)	Non-randomized trial	Healthy adults	Moderate	Table 2;Supplemental Table 2
Hallert, 2003(41)	Non-randomized trial	Adults with UC	Moderate	Table 2;Supplemental Table 4
Nylund, 2020(90)	Observational	Adults with CeD and non-CeD with gluten sensitivity	Moderate	Supplemental Table 5
Queenan, 2007(57)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Van den Abbeele, (44)2018	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Kristek, 2019(45)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Hughes, 2008(58)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Gamage, 2017(59)	*in vitro*	Healthy pediatric population	Reliable w/o restrictions	Supplemental Table 7
Connolly, 2010(46)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Brahma, 2017(60)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Titgemeyer, 1991(61)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Roye, 2019(62)	*in vitro*	Healthy adults	Reliable w/ restrictions	Supplemental Table 7
Connolly, 2012(47)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Nordlund, 2012(63)	*in vitro*	Healthy adults	Reliable w/ restrictions	Supplemental Table 7
Lebet, 1998(64)	*in vitro*	Healthy adults	Reliable w/ restrictions	Supplemental Table 7
Kim, 2009(48)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Pham, 2018(65)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Tsitko, 2019(49)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Hernot , 2008(50)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Wood, 2002(51)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Yang, 2013(53)	*in vitro*	Healthy adults and with obesity	Reliable w/o restrictions	Supplemental Table 7
Kedia, 2009(52)	*in vitro*	Healthy adults	Reliable w/ restrictions	Supplemental Table 7
Slade, 1987(54)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Dong, 2020(66)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Glei, 2020(67)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Akkerman, 2020(55)	*in vitro*	Healthy pediatric population	Reliable w/o restrictions	Supplemental Table 7
Wang, 2021(56)	*in vitro*	Healthy adults	Reliable w/o restrictions	Supplemental Table 7
Duysburgh, 2021(35)	*in vitro*	Adults with elevated cholesterol	Reliable w/o restrictions	Supplemental Table 7
Oat intake and GI symptoms				
Cicero, 2020(69)	RCT	Adults with elevated cholesterol	Some Concern	Supplemental Table 1
Keenan, 1991(68)	RCT	Adults with elevated cholesterol	High	Supplemental Table 1
Hakkola, 2020(70)	RCT	Healthy adults	Some Concern	Supplemental Table 1
Pitkala, 2007(71)	RCT	Elderly	Some Concern	Supplemental Table 1

Berggren, 2008(34)	RCT	Healthy pediatric population	Some Concern	Supplemental Table 1
Kemppainen, 2008(79)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Peraaho, 2004(77)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Lionetti, 2018(78)	RCT	Pediatric population with CeD	Some Concern	Supplemental Table 3
Nyman, 2020(39)	RCT	Adults with UC	Some Concern	Supplemental Table 3
Sturtzel, 2010(72)	Non-randomized trial	Elderly	Moderate	Supplemental Table 2
Valle-Jones, 1985(73)	Non-randomized trial	Elderly	Moderate	Supplemental Table 2
Paruzynski, 2019(74)	Non-randomized trial	Healthy pediatric population	Low	Supplemental Table 4
Storsud, 2003a(82)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Storsud, 2003b(81)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Lundin, 2003(85)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Baker, 1976(84)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Sey, 2011(83)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Kajs, 1997(75)	Non-randomized trial	Healthy adults	Moderate	Supplemental Table 4
Hallert, 2003(42)	Non-randomized trial	Adults with UC	Moderate	Supplemental Table 4
Hoffenberg, 2000(80)	Non-randomized trial	Pediatric population with CeD	Moderate	Supplemental Table 4
Van Kruiningen, 2005(92)	Observational	Families with Crohn's disease	Moderate	Supplemental Table 5
Tapsas, 2007(87)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Janatuinen, 2002(88)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Kaukinen, 2013(91)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Nylund, 2020(90)	Observational	Adults with CeD and non-CeD with gluten sensitivity	Moderate	Supplemental Table 5
Tuire, 2012(86)	Observational	Adults with CeD	Moderate	Supplemental Table 5

Oat supplementation and histopathological/immunological changes

Kemppainen, 2008(79)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Hogberg, 2004(95)	RCT	Pediatric population with CeD	Some Concern	Supplemental Table 3
Peraaho, 2004(77)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Lionetti, 2018(78)	RCT	Pediatric population with CeD	Some Concern	Supplemental Table 3
Holm, 2006(96)	RCT	Pediatric population with CeD	High	Supplemental Table 3
Janatuinen, 1995(93)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Sjoberg, 2014(99)	RCT	Pediatric population with CeD	Some Concern	Supplemental Table 3
Hollen, 2006(98)	RCT	Pediatric population with CeD	Some Concern	Supplemental Table 3
Koskinen, 2009(97)	RCT	Pediatric population with CeD	High	Supplemental Table 3
Janatuinen, 2000(94)	RCT	Adults with CeD	Some Concern	Supplemental Table 3
Hoffenberg, 2000(80)	Non-randomized trial	Pediatric population with CeD	Moderate	Supplemental Table 4
Storsud, 2003b(81)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Srinivasan, 1999(102)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Lundin, 2003(85)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Dissanayake, 1974(100)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Sey, 2011(83)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Cooper, 2013(103)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Hardy, 2014(106)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Emanuel, 2007(107)	Non-randomized trial	Pediatric population with CeD	Moderate	Supplemental Table 4
Srinavasan, 2006(104)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Srinavasan, 1996(101)	Non-randomized trial	Adults with CeD	Moderate	Supplemental Table 4
Janatuinen, 2002(88)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Kempainen, 2007(105)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Tuire, 2012(86)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Kaukinen, 2013(91)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Aaltonen, 2017(89)	Observational	Adults with CeD	Moderate	Supplemental Table 5
Arentz-Hansen, 2004(111)	*in vitro*	Adults with CeD	Reliable w/ restrictions	Supplemental Table 6
Picarelli, 2000(108)	*in vitro*	Adults with CeD	Reliable w/o restrictions	Supplemental Table 6
Silano, 2014(115)	*in vitro*	Pediatric population with CeD	Reliable w/o restrictions	Supplemental Table 6

Hollen, 2003(110)	*in vitro*	Pediatric population with CeD	Reliable w/o restrictions	Supplemental Table 6
Maglio, 2011(113)	*in vitro*	Persons with CeD	Reliable w/o restrictions	Supplemental Table 6
Comino, 2011(114)	*in vitro*	Pediatric population with CeD	Reliable w/o restrictions	Supplemental Table 6
Kilmartin, 2003(109)	*in vitro*	Adults with CeD	Reliable w/o restrictions	Supplemental Table 6
Kilmartin, 2006(112)	*in vitro*	Adults with CeD	Reliable w/o restrictions	Supplemental Table 6

[1] RCT risk assessment categories are Low, Some Concern or High as categories while the non-randomized trials and, observational are rated as Low, Moderate and High and *in vitro* studies as Reliable w/o restrictions, Reliable w/ restrictions or Unreliable. [2] Study by Duysburgh, 2021 was an RCT with experimental component, thus we evaluated it as both, clinical and in vitro study. CeD, celiac disease; GI, gastrointestinal; RCT, randomized controlled trial; UC, ulcerative colitis

Table 2. Summary of clinical trials investigating the association between oat supplementation and changes in microbiome and microbiome GI metabolite status

Lead Author, Publication year	Study design	Study population characteristics			Characteristics of the trial			Microbiome				SCFAs			
		Population	Sample size	Health status	Intervention	Control	Duration (wks)	Between visit differences	Effect	Between group differences	Yes/no	Between visit differences	Effect	Between group differences	Yes/no
Duysburg, 2021 (35)	Cross-over RCT	Adults	34	Hypercholesterolemic	40g cooked old fashioned oats/d	40g cream of rice/d	6 (2 periods)	*Lactobacillus*	O	*Lactobacillus*	Λ				
								Bifidobacterium	O	*Bifidobacterium*	O				
Pino, 2021 (36)	RCT	Adults	37	Type 2 diabetes mellitus	5g oat β-glucan/d	5g cellulose/d	12	Total bacteria	V▲	n.a.	---				
								Firmicutes	V	n.a.	---				
								Bacteroidetes	V	n.a.	---				
								Verrucomicrobia	V▲	n.a.	---				
								Lactobacillus	V	n.a.	---				
								Bifidobacterium spp	V	n.a.	---				
								Akkermansia municiphalia	▲	n.a.	---				
								Butyrate producing bacteria	V▲	n.a.	---				
Ye, 2020[1] (37)	RCT	Adults	28	Hypercholesterolemic	80g oatmeal/d	80g white rice/d	45d	*Subdoligranulum*	Λ	n.a.	---				
								Blautia	Λ	n.a.	---				
								Erysipelactoclostridium	Λ	n.a.	---				
								Odoribacter	V	n.a.	---				
								Aliihoeflea	V	n.a.	---				
								Pelagibacterium	V	n.a.	---				
								Megamonas	▼	n.a.	---				

Martenso, 2005 (27)	RCT	Adult	56	Healthy	84g oat based/d or 84g ropy oat-based/d	84g condensed milk daily/d	8	Ropy oat-based: *Bifidobacterium*	Λ	Bifidobacteria	Λ
								Ropy oat-based:Total population	Λ	n.a	n.a
								Oat based intervention:Bifidobacteria	O	n.a	n.a
								Oat based intervention: Total population	O	n.a	n.a
								Bifidobacteria	▲	Bifidobacteria	O
								Enterobacteriaceae	▼	Enterobacteriaceae	O
								Sulphite-reducing clostridia	O	Sulphite-reducing clostridia	O
Berggren, 2003 (34)	RCT	Pediatric population	69	Healthy	100g oats fermented with *Lactobacillus plantarum*/d	100g oats/d	3 wk	Lactobacilli	↑	Lactobacilli	↑
Li, 2017 (43)	Non-randomized trial	Adult	26	Healthy	Oat	Rice	1	*Anaerotruncus colihominis*	V	n.a.	---
								Bacteroides cellulosilyticus	V	n.a.	---
								Bacteroides thetaiotaomicron	V	n.a.	---
								Bifidobacterium adolescentis	Λ	n.a.	---
								Clostridium asparagiforme	V	n.a.	---
								Clostridium leptum	V	n.a.	---
								Eubacterium eligens	V	n.a.	---

Study	Design	Population	N	Health status	Intervention	Control	Duration	Bacteria				Metabolite		Metabolite	
								Eubacterium ventriosum	V	n.a.	---				
								Gordonibacter pamelaeae	V	n.a.	---				
								Roseburia hominis	V	n.a.	---				
								Roseburia inulinivorans	V	n.a.	---				
								Ruminococcus callidus	V	n.a.	---				
								Ruminococcus torques	V	n.a.	---				
								Streptococcus thermophilus	V	n.a.	---				
Connolly, 2016 (28)	Cross-over RCT	Adult	32	Glucose intolerant or mild to moderate hypercholesterolaemic	45g whole grain oat granola/d	45g non-whole grain/d	6 (2 periods)	*Bifidobacterium*	Λ▼	n.a	n.a	Acetic acid	O	Acetic acid	O
								Lactobacillus	Λ	n.a	n.a	Propionic acid	O	Propionic acid	O
								Total population	Λ▼	n.a	n.a	Lactic acid	O	Lactic acid	O
								Bacteroides and *Prevotella*	O	n.a	n.a				
								Ruminococcus	O	n.a	n.a				
								Clostridium histolyticum/ perfringens	O	n.a	n.a				
								Atopobium	O	n.a	n.a				
Johansso, 1998 (29)	RCT	Adults	48	Healthy	3g oat fermented in *Lactobacillus plantarum*/d	Pure rose hip drink	3	*Bifidobacteria*	Λ▲	n.a	n.a	Total SCFA	Λ	n.a	n.a
								Lactobacillus	↑	n.a	n.a	Acetic acid	Λ	n.a	n.a
								Sulphite-reducing clostridia	V▼	n.a	n.a	Propionic acid	Λ	n.a	n.a

Study	Design	Population	N	Disease	Intervention	Comparator	Wk	Microbiota	Int	(comp)	Comp	Metabolite	Int	(comp)	Comp
								Anaerobes	O	n.a	n.a	Lactic acid	↑	n.a	n.a
								Aerobes	O	n.a	n.a				
								Gram-negative anaerobes	O	n.a	n.a				
								Enterobacteriaceae	O	n.a	n.a				
Nyman, 2020 (39)	RCT	Adults	130	UC	12g (6g β-glucan) dietary fiber from oat bran/d	5g (<0.5g β-glucan) dietary fiber from wheat/d	24					Total SCFA	∧	Total SCFA	O
												Acetic acid	O	Acetic acid	O
												Propionic acid	∧	Propionic acid	O
												i-Butyric acid	∧	i-Butyric acid	O
												Butyric acid	∧	Butyric acid	∧
												i-Valeric acid	O	i-Valeric acid	O
												Valeric acid	∧	Valeric acid	O
Tjellstrom, 2014[1] (39)	RCT	Pediatric population	69	CeD	25-50g oats/d with GFD	GFD	52					Total SCFA	▼	Total SCFA	↑
												Fermentation index	O	Fermentation index	O
												n.a	---	Acetic acid	↑
												n.a	---	n-Butyric acid	↑
												n.a	---	Propionic acid	O
												n.a	---	i-Butyric acid	O
												n.a	---	i-Valeric acid	O
												n.a	---	n-Valeric acid	O
Valeur, 2015 (41)	Non-randomized trial	Adults	10	Healthy	60g oatmeal/d	None	1					Total SCFA	O	n.a	---

								Acetic acid	O	n.a	---
								Propionic acid	O	n.a	---
								i-Butyric acid	O	n.a	---
								Butyric acid	O	n.a	---
								i-Valeric acid	O	n.a	---
								Valeric acid	O	n.a	---
Nillson, 2008 (40)	Non-randomized trial	Adults	25	Healthy	40g oat bran/d	None	12	Formic Acid	O	n.a	---
								Acetic acid	Λ	n.a	---
								Propionic acid	Λ	n.a	---
								Butyric acid	O	n.a	---
								i-Butyric acid	Λ	n.a	---
								i-Valeric acid	O	n.a	---
								Valeric acid	O	n.a	---
Hallert, 2003 (42)	Non-randomized trial	Adults	22	UC	60g of oat bran added to usual diet/d	Usual diet	12	Total SCFA	O	n.a	---
								Acetic acid	O	n.a	---
								Propionic acid	O	n.a	---
								i-Butyric acid	O	n.a	---
								Butyric acid	Λ	n.a	---

| | i-Valeric acid | O | n.a | --- |
| | Valeric acid | O | n.a | --- |

In case of comparison between the two visits (baseline vs post-intervention): ΛV indicates changes in intervention group, ▲ ▼ indicates changes in control group, ↑↓ indicates change in both groups; O indicates no difference reported.[1] Posthoc analysis following a trial. CeD, celiac disease; SCFA, short chain fatty acid; UC, ulcerative colitis