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**Feeding melancholic microbes:  
MyNewGut recommendations on diet and mood**

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**Abstract**

Depression is a highly prevalent disorder which exerts a major economic impact in all European countries. The brain-gut-microbiota axis has been described as a new paradigm for advancing understanding and treatment of the disorder. There is now over-whelming evidence to support the fact that gut microbes have a major impact on central neurochemistry and behaviour, especially stress related disorders such as depression. Recent studies indicate that patients with depression have a gut dysbiosis. The reason for this dysbiosis is uncertain. Over recent decades, dietary patterns in Europe and elsewhere have undergone major compositional changes, with increased intakes of red meat, high fat foods, and refined sugars. Individuals who consume a Mediterranean diet have lower rates of depression and a recent study suggests that a Mediterranean diet may have antidepressant properties. Assuming this to be the case, which components of the Mediterranean diet mediate the effects? Highly levels of polyphenols or polyunsaturated fatty acids are obvious candidates. We in the MyNewGut consortium recommend that patients with depression or vulnerability to depression should be encouraged to enhance a plant-based diet with a high content of grains /fibres and fish.

Keywords: MyNewGut, depression, gut microbiota, diet, dysbiosis

## 61 **Background**

62 Depression is not only the common cold of psychiatric disorders but one of the most  
63 prevalent medical conditions. In Europe the economic impact of depression  
64 accounts for one third of the cost of all psychiatric and neurological disease (1).

65 While several subtypes of mood disorder have been described the most important in  
66 terms of prevalence are major depression (unipolar) and bipolar affective disorder,  
67 previously called manic depression. The point prevalence of major depression in  
68 Europe is between 3% - 6% and it is clear that no society is immune to the disorder  
69 (2). Despite major investment in studies exploring the biology of depression, it  
70 remains a syndrome diagnosed by the presence of a cluster of symptoms (3) and not  
71 by objective laboratory investigations. Most, though not all cases of depression arise  
72 due to negative life events in a setting of psychosocial stress, with genetics and early  
73 life adversity frequently yielding vulnerability to the disorder. The core features of  
74 depression are low mood and/or anhedonia, the inability to feel enjoyment. Anxiety  
75 is often an important feature of major depression, though it can be a distinct  
76 disorder, often presenting as generalized anxiety disorder, panic disorder or  
77 obsessive compulsive disorder.

78 Current pharmacotherapy in Europe and elsewhere for treating major depression  
79 comprises the manipulation of monoaminergic systems (catecholaminergic and  
80 serotonergic systems). (4). Clinical efficacy of these drugs is limited by a delayed  
81 onset of action and a considerable proportion of patients (maybe as high as 40%)  
82 who do not respond adequately to treatment (5). Psychological therapies, likewise  
83 have limitations, and are used either on their own or in combination with  
84 medication. Cognitive behaviour therapy (CBT) and mindfulness are the most

85 widely used and studied psychological therapies. For many patients a combination  
86 of antidepressants and CBT/mindfulness is considered as the optimal therapy.

87 Over the past decade there has been a major focus on the role of inflammation in the  
88 pathophysiology of depression and in determining vulnerability to the disorder. It is  
89 established that major depression correlates with definite increases in pro-  
90 inflammatory cytokines such as interleukin-1 (IL-1), IL-8 and TNF-alpha (6). These  
91 cytokines potentially activate the hypothalamic-pituitary-adrenal axis (HPA) and may  
92 play a major part in maintaining the HPA over-activation seen in depression(7).  
93 Effective treatment of depression by whatever modality is accompanied by  
94 suppression of pro-inflammatory cytokines and decreased activation of the HPA. It  
95 is of interest from a nutritional perspective that a Mediterranean diet which is  
96 viewed as having anti-inflammatory effects is associated with less depression than  
97 standard northern European diets (8).

98 The FP7 EU project MyNewGut ([www.mynewgut.eu](http://www.mynewgut.eu)) is a five-year initiative (2013-  
99 2018) integrated by a highly multidisciplinary team that cooperates to disentangle  
100 the role played by our gut microbiota, via interactions with lifestyle factors (e.g. diet,  
101 eating habits, stress, etc.), in the regulation of pathways leading to the development  
102 of obesity and behavioural disorders. In this review the views of the Consortium in  
103 relation to diet and mood and how such effects are mediated by the microbiota are  
104 laid out.

105 **New paradigm in mental health**

106 The brain-gut-microbiota axis is the focus of the latest paradigm not just in neuroscience, but  
107 specifically in relation to mental health, and has been put forward as a potential watershed  
108 development (9). There is now an ever accumulating volume of evidence to support the fact  
109 that gut microbes have a major impact on central neurochemistry and behaviour, especially

110 stress related responses(10). In humans functional MRI (11) and electroencephalography(12)  
111 have been used to support animal studies. Through what mechanism(s) do gut microbes exert  
112 such significant central influence and how might targeting the brain-gut-microbiota axis  
113 through dietary intervention yield effective therapies for patients with depression?  
114 In reviewing the published literature on the brain-gut-microbiota axis and mental health the  
115 main limitation at this point is the paucity of well designed, adequately powered clinical  
116 studies. As has been pointed out elsewhere, a majority of papers so far published are from  
117 the pre-clinical arena (9). Drawing major clinical conclusions from rodent studies is  
118 problematic.

### 119 **Brain-gut microbe communication**

120 It is argued that gut microbe to brain communication is a black box of which we have limited  
121 understanding (13). However, this may be considered as an overly pessimistic analysis of the  
122 current state of knowledge. We know that the brain-gut-microbiota axis is a bidirectional  
123 communication system which enables gut microbes to communicate with the brain, and the  
124 brain in turn to communicate with the gut (14). While brain-gut communication has been the  
125 subject of research for decades an exploration of gut microbes as an important vehicle within  
126 this context has only recently been proposed. The mechanisms of signal transmission are  
127 complex and involve neural, endocrine, immune, and metabolic pathways. Preclinical studies  
128 have implicated the vagus nerve, that long meandering nerve, as a fundamental neural route  
129 of communication between gut microbes in the periphery and centrally-mediated behavioural  
130 effects, as demonstrated by the elimination of central *Lactobacillus rhamnosus* (JB1) effects  
131 following a full truncal vagotomy (15). Epidemiological studies have demonstrated that  
132 individuals who underwent a full truncal vagotomy for treatment of peptic ulcer disease have  
133 a diminished risk of Parkinson's disease as they age (16). The gut microbiota also regulates

134 brain monoamines, such as serotonin, by altering levels of precursors; for example  
135 *Bifidobacterium longum* 35624 has been shown to increase plasma tryptophan levels and thus  
136 impact central 5-HT (17). Tryptophan is the amino acid precursor of serotonin and the  
137 human brain has limited storage capacity, therefore requiring a continuous supply from the  
138 periphery. This supply originates from both a dietary source and from intestinal  
139 bifidobacteria who can synthesise the molecule.

140 Intriguingly, many gut bacteria can synthesise and release neurotransmitters. *Lactobacillus*  
141 and *Bifidobacterium* species produce gamma-aminobutyric acid (GABA): *Escheridia*,  
142 *Bacillus* and *Saccharomyces spp.* produce noradrenaline: *Candida*, *Streptococcus*,  
143 *Escheridia* and *Enterococcus spp.* can produce 5-HT: *Bacillus* can produce dopamine: and  
144 *Lactobacillus* can produce acetylcholine (18, 19). These gut-originated neurotransmitters can  
145 cross the mucosal layer of the intestine, though it is highly unlikely they directly influence  
146 brain chemistry. Even if they enter the blood stream, which has not been demonstrated, they  
147 cannot cross the blood brain barrier (BBB). Their impact on brain function therefore is most  
148 likely to occur by acting locally on the enteric nervous system. Short chain fatty acids  
149 (SCFAs), which include butyrate, propionate and acetate are metabolic products of gut  
150 microbial activity and are a rich energy source. They can exert central effects either through  
151 conventional GPCRs (G-protein coupled receptors), though such receptors are sparsely  
152 concentrated in the mammalian brain and the half-life of SCFAs is exceedingly short in the  
153 plasma. Alternatively, they may behave as epigenetic modulators by inhibiting histone  
154 deacetylases (HDACs)(20). The immune system provides another gut to brain  
155 communication pathway, signalling by way of cytokine molecules (21). Such molecules  
156 produced at the level of the gut can travel via the bloodstream to the brain. However, in  
157 normal physiological circumstances they do not cross the BBB, but there is accumulating  
158 evidence to support the view that they signal across the BBB and influence brain regions such

159 as the paraventricular nucleus of hypothalamus and circumventricular organs where the BBB  
160 is deficient. If plasma levels of the cytokines IL-1 and IL-6 are elevated by infection or  
161 otherwise they activate the core stress system, the HPA, bringing about the release of cortisol.  
162 This is viewed as the most potent activating mechanism of the stress system and is of special  
163 relevance in disorders such as the depression that emerges with interferon therapy for  
164 hepatitis or melanoma (22).

### 165 **Psychopathology and gut dysbiosis**

166 There is increasing evidence that some psychiatric disorders such as depression may be  
167 associated with a gut dysbiosis, a microbial imbalance. The extent to which such a dysbiosis  
168 is central to the pathophysiology of depression has yet to be fully elucidated.

### 169 **Depression**

170 Lyte et al (23) found that oral gavage of the pathogen *Campylobacter jejuni*, in tiny  
171 subclinical doses, which failed to exert an immune response, resulted in anxiety-type  
172 behaviour in rodents. They also found that areas of brainstem, such as the nucleus tractus  
173 solitarius and lateral parabrachial nucleus, are involved in the processing that results in the  
174 autonomic, neuroendocrine and behavioural responses induced by the gavage.

175 A recently published epidemiological analysis supports the link between gut infection and  
176 anxiety. Bruch analysed the Medical Expenditure Panel Survey (MEPS) to prospectively  
177 determine a relationship between intestinal infection and future onset of an anxiety disorder  
178 (24). The data for all respondents who were 18 years of age or older and who did not have an  
179 anxiety disorder at baseline were included. Within the study population, there were 2577  
180 subjects with an intestinal infection in Round 1 and 4239 with an anxiety disorder  
181 commencing subsequently. In total an intestinal infection in Round 1 was associated with a



182 significantly increased odds ratio of a subsequent emergent anxiety disorder. This major  
183 epidemiological study provides solid evidence for a link between intestinal infection and the  
184 development of anxiety.

185 O'Mahony and colleagues studied the gut microbiota in a maternal separation model of  
186 depression in rats (25). They reported an elevation in corticosterone in such animals,  
187 together with an increase in pro-inflammatory cytokines and a decrease in the diversity of gut  
188 microbes. In a recent study the fecal microbiota was sequenced in a depression study (26).  
189 Forty-six patients with depression and 30 healthy controls were recruited. High-throughput  
190 pyrosequencing showed that, according to the Shannon index, increased faecal bacterial  
191 alpha-diversity was present in those currently depressed but not in a group who had  
192 responded to treatment. This suggests that increased alpha diversity is a state rather than trait  
193 marker for depression. Bacteroidetes, Proteobacteria, and Actinobacteria were increased,  
194 whereas Firmicutes were significantly decreased. Despite the profound inter-individual  
195 variability, levels of several predominant genera differed between the depressives and  
196 controls. The depressives had increased levels of Enterobacteriaceae and Alistipes but  
197 reduced levels of Faecalibacterium. The authors conclude that further studies are necessary to  
198 elucidate the temporal and causal relationships between gut microbiota and depression and to  
199 evaluate the suitability of the microbiome as a biomarker. In a study conducted at APC  
200 Microbiome Ireland depressed patients had elevated cortisol output together with decreased  
201 faecal microbial richness and surprisingly when rats were given a humanised microbiota from  
202 depressed patients, as opposed to healthy controls, they developed a depressive phenotype  
203 from both a behavioural and immune perspective(27).

#### 204 **Depression co-morbidity**

205 Depression is frequently co-morbid with a variety of medical illnesses including  
206 cardiovascular disease, metabolic syndrome and the gastrointestinal disorder irritable bowel  
207 syndrome (IBS), which presents with abdominal pain or discomfort and an alteration of  
208 bowel habit in the absence of gross pathology. In IBS an increase in pro-inflammatory  
209 cytokines in the plasma has been reported(28) together with altered gut barrier function (29).  
210 The latter is thought to lead to a ‘leaky gut’ and the passage of inflammatory molecules such  
211 as lipopolysaccharide (LPS) from gram negative bacteria into the blood stream(30) with  
212 subsequent activation of the immune system via toll-like receptors. The maternal separation  
213 model of IBS supports the view of an altered gut microbiota in the condition together with a  
214 pro-inflammatory phenotype.

215 It is possible that a poor quality diet may bring about the altered microbiota observed in  
216 depression. Narrowing of dietary diversity with reduced intake of essential nutrients can  
217 reduce availability of substrates for specific microbial growth and this could contribute to the  
218 intestinal dysbiosis of depression.

### 219 **Diet and the microbiota**

220 Over recent decades, dietary patterns in Europe and elsewhere have undergone major  
221 compositional changes, with increased intakes of red meat, high fat foods, and refined sugars.  
222 This ‘Westernization’ of diets together with sedentary lifestyles results in modifications to the  
223 gut microbiota, which may at least partially contribute to the increasing incidence of chronic  
224 inflammatory disorders, such as cardiovascular disease, obesity, inflammatory bowel disorder  
225 and depression (31). If we are to improve the nutritional value of food and positively impact  
226 mental health, we need to more fully understand the biological interactions between the food  
227 and microbiota. Many human studies have assessed dietary impact on the gut microbiota but  
228 they are limited by the difficulties in controlling potential confounding variables especially

229 lifestyle behaviours. Studies are limited by the fact that the microbiota is sequenced from  
230 faecal samples which provides no detail of the microbiota in various gut regions. With these  
231 limitations in mind we have learned some useful lessons in relation to dietary patterns and  
232 microbiota composition.

### 233 **Mediterranean diet and depression**

234 There is increasing evidence to support the view that poor quality diet is a risk factor for  
235 major depression. Epidemiological studies have long demonstrated that those on a  
236 Mediterranean diet suffer from less depression (32). Diets rich in fruit, vegetables, grains and  
237 fish seem protective against depression while a diet of highly processed food and those with  
238 a high sugar content predispose to depression(33). However, the data upon which these  
239 conclusions are based are largely observational. There is a paucity of properly controlled  
240 studies.

241 A recent study from Australia used a randomized controlled trial (RCT) design to investigate  
242 the efficacy of a dietary program for the treatment of major depression(34). A structured  
243 dietary support, focusing on improving diet quality using a modified Mediterranean diet was  
244 compared to a social support control condition. Sixty-seven patients were recruited fulfilling  
245 criteria for major depression and scoring 75 or less, out of a possible score of 104, on a  
246 Dietary Screening Tool, a score which indicated a poor baseline diet. If patients were on  
247 antidepressant medication or undergoing psychotherapy, they were required to be on the  
248 same treatment for at least 2 weeks prior to study entry. The dietary intervention group  
249 showed a significantly greater improvement in depression scores between baseline and  
250 12 weeks than the social support control group. Overall, the results of this trial suggest that  
251 improving diet may be a useful strategy for treating depression or at least as an adjunctive to  
252 conventional therapies. Another study by Forsyth and colleagues reaches similar

253 conclusions(35). Furthermore, evidence is accumulating to support the view that the way in  
254 which diet impacts health in general is mediated by the gut microbiota(36, 37).

255 If we assume that a Mediterranean diet is effective in the prevention and perhaps the  
256 treatment of depression, what components of such a diet mediate these effects?

### 257 **Polyunsaturated fatty acid and mood**

258 The brain is a lipid-rich organ containing mostly complex polar phospholipids, sphingolipids,  
259 gangliosides and cholesterol (38). These are involved in both the morphology and physiology  
260 of neurones. The glycerophospholipids in the brain contain a high proportion of  
261 polyunsaturated fatty acids (PUFA) derived from the essential fatty acids, linoleic acid and  
262 alpha-linolenic acid. The main PUFAs in the brain are docosahexaenoic acid (DHA) derived  
263 from the omega 3 fatty acid, alpha-linolenic acid, and arachidonic acid and docosatetraenoic  
264 acid, both derived from the omega 6 fatty acid, linoleic acid(39).

265

266 Omega-3 fatty acid is derived from fish oil and there is considerable epidemiological  
267 evidence to indicate that those with a diet rich in fish have a lower incidence of  
268 cardiovascular disease than those with other diets(40). In recent times, the focus of attention  
269 has been on the impact of omega-3 fatty acids on depression. Studies indicate that in  
270 countries where there is a high consumption of fish there are lower rates of depression(41).  
271 However, in many European countries in recent decades the intake of omega-3 PUFAs has  
272 declined with a concomitant increase in omega-6 PUFA intake(42). Hibbeln was one of the  
273 first to draw demonstrate the importance of omega-3 PUFAs in mental health: in a cross-  
274 national study he found a significant negative correlation between worldwide fish  
275 consumption and prevalence of depression (43). Subsequent studies have found altered  
276 omega-6/omega-3 ratios in the plasma of depressed patients (44) and altered red blood cell

277 phospholipids (45). In post-mortem brain tissue lower DHA levels have been found in the  
278 orbitofrontal cortex of in depressed patients.

279 Nemets and colleagues studied 22 depressed patients who failed to respond to antidepressant  
280 therapy(46). The study had a parallel group, double-blind design in which EPA or placebo  
281 was added to the on-going antidepressant. A significant effect of omega-3 compared with  
282 placebo was found by week three of treatment. Peet et al examined the effects of EPA in 70  
283 patients who had antidepressant resistant depression (47). Patients were randomised to  
284 receive either placebo or EPA in doses of 1, 2 or 4 grams per day for 12 weeks. They  
285 continued their antidepressant throughout. Forty-six of the 52 patients receiving the EPA and  
286 14 of the 18 patients receiving placebo completed the 12 weeks study. The 1 gram per day  
287 group showed a significantly better outcome than the placebo group. The authors conclude  
288 that EPA 1 gram per day is an effective strategy for augmenting antidepressants in those who  
289 are treatment resistant.

290 The results with DHA are inconclusive. Thirty-six subjects with major depression assigned to  
291 receive DHA (2 g/d) for 6 weeks did not show differences in the score of the Montgomery-  
292 Asberg Depression Rating Scale compared with the placebo-treated group (48). A number of  
293 open label studies without appropriate controls report benefits. Given the lack of a placebo  
294 control, these results need to be viewed with caution (49) .

295 A recent meta-analysis of fifteen trials (916 total participants) using omega-3 PUFAs as  
296 either a mono or adjunctive therapy were analysed. Studies were selected based on  
297 prospective, randomized, double-blinded, placebo-controlled study design, if depressive  
298 episode was the primary complaint with or without comorbid medical conditions and, if  
299 appropriate outcome measures were used to assess depressed mood (50). This meta-analysis  
300 concluded that n-3 PUFA supplements with >60% of EPA (in a dose range of 200 to 2200

301 mg/d in excess of DHA) ameliorated the clinical condition. However, doses containing  
302 primarily DHA or <60% EPA were not effective against primary depression.  
303 It is known that EPA has a general immuno-suppressive effect with a capacity to suppress  
304 inflammatory states. This may be relevant in the context of depression which is known to be  
305 associated with an increase in the acute phase protein C-reactive protein (CRP) and pro-  
306 inflammatory cytokines. A recent study demonstrated the capacity of polyunsaturated fatty  
307 acids to impact the brain-gut axis by increasing levels of bifidobacteria (51). At this point it  
308 seems reasonable to recommend fish in the diet of patients with depression but there is  
309 insufficient data to recommend omega-3 PUFAs as either a mono or adjunctive therapy in the  
310 disorder.

### 311 **Probiotics and depression**

312 Fermented foods have long been associated with a health benefit but only recently has that  
313 benefit been extended to mental health. Numerous claims of therapeutic efficacy have been  
314 made for probiotics but most claims are not substantiated by rigorous placebo controlled  
315 studies. Psychobiotics are defined as bacteria which when ingested in adequate amounts have  
316 a positive mental health benefit (52).

317 One therapeutic area where the benefits of probiotics have been established is in the common  
318 gastrointestinal disorder IBS. Several placebo controlled studies indicate that a bifidobacteria  
319 is highly effective in treating the condition(53). This is of relevance given the fact that up to  
320 40% of patients with IBS have co-morbid depression and many bifidobacteria have anti-  
321 inflammatory activity.

322 The principal rationale for the use of probiotics in treating major depression rests on their  
323 potential for suppressing the pro-inflammatory component of depression. Can  
324 probiotics/psychobiotics alter this aberrant immunology? It was shown that a bifidobacteria  
325 in IBS switched the balance from a pro- to an anti-inflammatory cytokine response (54).

326 They found that in response to bifidobacteria treatment there was an increase in anti-  
327 inflammatory IL-10 and a reduction in pro-inflammatory IL-12 activity. Similar findings  
328 have been reported with *Lactobacillus acidophilus* (55).

329 There are several animal models of depression used for drug development. Using the  
330 maternal separation model, *Bifidobacterium longum* 35624 was found to normalise behaviour  
331 (17) and reduce corticosterone levels. This may indicate that the specific bifidobacteria strain  
332 has an antidepressant action.

333 In a recent study, Benton and colleagues used a placebo controlled design to examine the  
334 impact of probiotics on mood in healthy community based subjects. One-hundred and thirty-  
335 two subjects with a mean age of 62 years were recruited(56). Over a three week period they  
336 consumed either milk containing a probiotic or placebo daily. Mood was assessed at baseline  
337 and after 10 and 20 days of treatment. Those who rated their mood as poorest at baseline  
338 reported on average an improvement on probiotic by the end of the study. This improvement  
339 was not noted on placebo. Whether these findings translate to a clinical sample remains to be  
340 seen.

341 The effects of *Lactobacillus rhamnosus* HN001 given in pregnancy and postpartum on  
342 symptoms of maternal depression and anxiety in the postpartum period was assessed (57).

343 Two hundred and twelve women were randomised to HN001 and 211 to placebo. Women  
344 who received HN001 had significantly lower depression and anxiety scores in the postpartum  
345 period. The results strongly support the view that the psychobiotic is protective against the  
346 emergence of postpartum symptoms. This is the best human intervention study so far in the  
347 literature.

348 Overall, it seems reasonable to conclude that psychobiotic studies in depressed patients are  
349 urgently required.

350 **Prebiotics and depression**

351 Prebiotics are fibres metabolised by the microbiota and capable of increasing the levels of  
352 good bacteria such as bifidobacteria. Prebiotics are found in vegetables such as celery,  
353 Jerusalem artichoke, garlic etc. A number of small clinical controlled trials have assessed the  
354 efficacy of certain prebiotics on psychological outcomes with promising results. Schmidt and  
355 colleagues demonstrated that 3-week supplementation with a galactooligosaccharide (GOS)  
356 prebiotic, which has been shown to stimulate bifidobacterial growth, in healthy volunteers  
357 significantly reduced waking cortisol response, the stress hormone strongly linked to anxiety  
358 and depression (58). Moreover, a B-GOS cohort demonstrated altered behavioural outcomes  
359 through a decrease in attentional vigilance to negative versus positive information in a dot-  
360 probe task compared to placebo. It is interesting to note, however, that fructooligosaccharide  
361 (FOS) supplementation had no effect. These results suggest that shaping of microbiota  
362 composition through prebiotic intake could influence behavioural outcomes. In humans,  
363 prebiotic supplementation with trans-GOS not only enhanced bifidobacterial growth and  
364 improved bloating symptoms, but in addition significantly reduced anxiety scores in IBS  
365 sufferers (59).

### 366 **Polyphenols**

367 Polyphenols are undoubtedly the most numerous among the groups of phytochemicals  
368 present in plants. They are broadly divided into flavonoids and non-flavonoids. Resveratrol  
369 which is found in red wine has potent CNS actions. In an animal model of depression it has  
370 been shown to reduce depressive type behaviours while attenuating the release of both  
371 corticosterone and pro-inflammatory cytokines (60). It also exerts anti-oxidant activity acting  
372 through sirtuins, is known to be metabolised by the microbiota and influences the  
373 Firmicutes/Bacteroidetes ratio in the intestine (61). To date there are no published controlled  
374 trials of resveratrol in depressed patients.



375 The polyphenol natural product curcumin possesses a variety of biological and  
376 pharmacological properties. Curcumin was found to reduce salivary cortisol levels in  
377 depressed patients relative to that seen in the placebo group(62). Recent data also indicates an  
378 impact in increasing gut microbial diversity (63).

### 379 **MyNewGut Consortium recommendations**

380 The Mediterranean diet is associated with lower rates of depression, impacts optimally on the  
381 gut microbiota and increasing evidence indicates that such a diet has antidepressant  
382 effects(64). Patients with depression or vulnerability to depression should be encouraged to  
383 enhance a plant-based diet with a high content of grains and fibres. High fibre diets are  
384 associated with fewer symptoms of depression. When analyzed by the source of fiber, diets  
385 higher in total fiber (more than 27 grams per day), and fiber from vegetables and  
386 breads/cereals (mostly whole grain) were associated with a 42%, 46%, and 41% reduced  
387 likelihood of having depressive symptoms, respectively(65). A decreased consumption of  
388 red, meat especially of processed meat(66), a regular intake of fish(67) and fermented  
389 foods(68) should be recommended. The intake of sodium and refined sugar should be  
390 restricted. Vigorous aerobic exercise consistent with the age and physical health of the patient  
391 should be encouraged(69).

### 392 393 **Author contributions**

394 TGD drafted the original manuscript. All authors contributed to discussion, editing and  
395 approval of the final manuscript.

### 396 397 **Conflicts of interest**

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### **Figure Legends**

576 Fig. 1 Shows how stress and poor diet combine to produce a gut dysbiosis and the symptoms  
577 of depression

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579 Fig. 2 Shows foods with high prebiotic content and capable of stimulating the growth of  
580 'good' bacteria