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**Interaction between diet and microbiota in the pathophysiology of Alzheimer's disease: focus
on polyphenols and dietary fibres**

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28 **ABSTRACT**

29 Animal studies increasingly indicate that the gut microbiota composition and function can be
30 involved in the pathophysiology and progression of Alzheimer’s disease (AD) at multiple levels.
31 However, few studies have investigated this putative gut-brain axis in human beings, and none of
32 them considered diet as a determinant of intestinal microbiota composition. Epidemiological studies
33 highlight that a high intake of fruit and vegetables, such as that typical of the Mediterranean diet,
34 can modulate AD progression. Thus, nutritional interventions are being increasingly studied as a
35 possible non-pharmacological strategy to slow down the progression of AD. In particular,
36 polyphenols and fibers represent the nutritional compounds with the higher potential of
37 counterbalancing the pathophysiological mechanisms of dementia due to their antioxidant,
38 antiinflammatory and antiapoptotic properties. These actions are mediated by the gut microbiota,
39 that can transform polyphenols and fibers into biologically active compounds including, among
40 others, phenyl- γ -valerolactones, urolithins, butyrate and other short-chain fatty acids (SCFAs). In
41 this review, the complex mechanisms linking nutrition, gut microbiota composition and
42 pathophysiology of cognitive decline in AD are discussed, with a particular focus on the role of
43 polyphenols and fibers. The gaps between pre-clinical and clinical studies are particularly
44 emphasized, as well as the urgent need for studies comprehensively evaluating the link between
45 nutrition, microbiome and clinical aspects of AD.

46

47 **KEY WORDS:** cognitive impairment; aging; short-chain fatty acids; butyrate

48 **1. Introduction: Alzheimer's disease and diet**

49 A large body of evidence linking dietary patterns with cognitive function in aging has emerged
50 from population-based studies in recent years [1, 2]. Namely, in older community-dwellers higher
51 adherence to Mediterranean-style diet has been associated with better cognitive performance [3, 4],
52 lower frequency of subjective cognitive complaints [5], lower prevalence and incidence of mild
53 cognitive impairment (MCI) and dementia [6, 7]. Host-related genetic factors, ethnicity and gender
54 can modulate these associations, but do not substantially modify the assumption that a healthy
55 dietary pattern has a positive influence on the pathophysiology of Alzheimer's disease (AD) and
56 other types of dementia [8, 9].

57 The Mediterranean diet is a dietary model which has been widely studied for the pivotal role in the
58 maintenance of the health status and the prevention of several disease risk factors [10], among
59 which neurological disorders [11]. The daily and abundant consumption of plant-based food groups,
60 as fruit, vegetables, cereals, and pulses leads to the intake of several nutrients that exhibit
61 biologically activities on homocysteine metabolism (B-group vitamins), oxidative stress (vitamin C,
62 vitamin E), neural inflammation, degeneration and plasticity (vitamin D, n-3 fatty acids) [12, 13].
63 Such foods are also a great source of non-nutrient bioactive compounds, like polyphenols, with
64 antioxidant, anti-inflammatory and putative neuroprotective properties [14-16]. Not only the
65 Mediterranean Diet, but also the adherence to other dietary patterns in which the intake of such
66 nutrients and bioactives is particularly emphasized and with reduced intakes of rapidly digested
67 carbohydrates, saturated fatty acids and salt, like the Mediterranean-DASH for Neurodegenerative
68 Delay (MIND) diet or the NU-AGE diet, is associated with better cognitive performance and slower
69 age-related cognitive decline [17, 18].

70 The ketogenic diet, with very low carbohydrate and high lipid content, has also gained attention for
71 its potential neuroprotective action, especially in the prodromal phases of AD [19, 20]. Despite the
72 promising findings resulted by *in vitro* and animal studies, mainly on the effects of ketones on the
73 mitochondria and their cellular energy-related functions, there still is a lack of clinical studies, as

well as a low quality of evidence from the few running ones, to recommend these diets for the prevention of dementia [21, 22].

Conversely, the presence of malnutrition in older age, with insufficient energy and micronutrient intake, is a well-established risk factor for the onset and progression of MCI and dementia [23, 24].

Diets including an excessive intake of animal proteins, saturated fatty acids and rapidly digested carbohydrates, are also associated with higher risk of MCI and dementia, and with increased cerebral β -amyloid deposition [25, 26]. Interestingly, recent evidence from animal models also links excessive salt intake with progression of dementia through promotion of tau phosphorylation, a central mechanism of neurodegeneration [27].

Despite the evidence from epidemiological and preclinical studies, the effective role of nutrition in the prevention and treatment of neurodegenerative disorders is far from being fully understood. Nutritional interventions for primary or secondary prevention of AD in older subjects have shown only limited benefits, and, to date, diet has only a secondary role in the clinical management of dementia [12, 28, 29]. Apart from methodological and ethical issues making the design of specific trials in this field very challenging, there are also other elements that must be considered, among which the impact of food intake on the whole organism, by starting from the digestive tract where nutrients are metabolized and absorbed.

In fact, diet represents one of the main factors contributing to shape the intestinal microbiota composition and function. Conversely, the microbiota of each individual interacts with food compounds in a complex way, influencing the whole physiology of the host. The microbiota can also influence the pathophysiology of dementia through multiple mechanisms [30, 31], and for these reasons the relationship between diet and dementia should be absolutely unraveled by also considering the key role of the gut microbiota and its metabolic activity.

Unfortunately, the interplay between diet, microbiota composition and cognitive function has not been comprehensively studied to date. The current state of knowledge allows to hypothesize that dietary patterns can modulate the pathophysiology of AD through mediation of the gut microbiota,

100 and that the consumption of certain types of foods can positively modulate cognitive function only
101 in the presence of specified microbiota composition. However, these assumptions are supported
102 only by indirect evidence, mainly coming from preclinical and animal studies. The aim of this
103 review is to discuss the most recent advances in this field, with a particular focus on how dietary
104 polyphenols and fibers can influence the pathophysiology of AD through mediation by the intestinal
105 microbiota.

106

107 **2. The gut-brain axis and Alzheimer's disease: pathophysiological mechanisms**

108 The term “gut-brain axis” is commonly used to describe a bidirectional channel of communication
109 between the gastrointestinal tract and the central nervous system (CNS). More recently, this term
110 has been extended to “microbiota-gut-brain axis”, in light of the accumulating evidence obtained
111 from germ-free animals as well as probiotics, antibiotics, and infection studies on the impact of the
112 intestinal microbiota on this gut-brain interaction [32].

113 Several neural, immune, endocrine, and metabolic pathways of communication between the gut
114 microbiota and the CNS have been proposed. Undoubtedly, one of the most important is mediated
115 by the vagus nerve, which conveys information between the gastrointestinal tract and the CNS in
116 both afferent and efferent direction [33]. Relatedly, several microbial-derived intermediates,
117 including short-chain fatty acids (SCFAs) and tryptophan metabolites [34, 35], interact with
118 enteroendocrine cells, enterochromaffin cells and the mucosal immune system, and might propagate
119 bottom-up signaling via vagal and/or spinal afferents [36-38]. In addition, some of these microbial-
120 derived molecules cross the intestinal barrier, entering portal and then systemic circulation, and
121 might even reach brain sites directly [36-38]. The microbiota can also produce or contribute to the
122 production of several neuroactive molecules including gamma-aminobutyric acid, serotonin,
123 norepinephrine, and dopamine [39-42]. Yet, it is unclear whether these neurotransmitters reach
124 relevant receptors in the brain or achieve sufficient levels to induce CNS responses.

125 In the past decade, advances in sequencing technology, metabolomics, and neurophysiology have
126 allowed a deeper investigation of the cross-talk between the gut and the CNS via the microbiota
127 both in health and disease states [43, 44]. An involvement of gut microbiota in the pathogenesis of
128 neurodegenerative diseases, including AD, has thus been hypothesized [45, 46]. The association
129 between gut microbiota and AD might be related to the central role of inflammation in the
130 development and progression of this neurodegenerative disorder [47]. Indeed, the gut microbiota is
131 a source of a large amount of amyloids - though different in their primary structure from the
132 amyloids in the CNS – lipopolysaccharides, and other toxins that may contribute to systemic

inflammation and disruption of physiological barriers [48]. Bacteria and/or their products can then migrate from the gastrointestinal tract to the CNS, especially in older subjects, where gut mucosa permeability tends to increase. In the CNS, bacterial products might promote neuronal amyloid aggregation and neuro-inflammation, ultimately leading to neural injury and degeneration [44, 45, 49, 50]. For example, rats exposed to bacterial amyloids displayed increased neuronal alpha-synuclein deposition in both the gut and the brain, enhanced microgliosis and astrogliosis, and increased central levels of proinflammatory cytokines compared to rats exposed to bacteria without the ability to produce amyloids [51].

Animal models have also been useful for gaining a better understanding of the relationship between microbiota dysbiosis and AD-like pathology. For example, in a series of elegant studies using β -amyloid precursor protein (APP) transgenic mice, a well-established preclinical model of AD, analysis of bacterial 16S rRNA from fecal samples revealed significant changes in gut microbial composition of transgenic mice compared to wild-type counterparts [52]. Remarkably, germ-free APP transgenic mice exhibited a less severe cerebral β -amyloid pathology compared with control mice with intestinal microbiota, suggesting that the absence of microbiota may retard the progression of AD-like pathology [52]. Intriguingly, colonization of germ-free APP transgenic mice increased cerebral β -amyloid to a greater extent when the microbiota originated from conventionally-raised APP transgenic mice compared with wild-type mice [52].

Supporting these findings, another study in APP transgenic mice revealed a shift in microbial composition compared to wild-type mice, as shown by the higher abundance of *Helicobacteraceae* and *Desulfovibrionaceae* at the family level and *Odoribacter* and *Helicobacter* at the genus level, and the lower abundance of *Prevotella* [53]. Notably, AD-related histological (i.e., amyloid plaque burden) and behavioral (i.e., impaired spatial learning and memory) features were found to be correlated with the specific microbiome state of animal models [53]. A subsequent study investigated age-related changes in the microbiota of APP transgenic mice and found that AD pathology shifted gut microbiota composition during ageing towards an inflammation related

159 bacterial profile (i.e., *Proteobacteria* and *Erysipelotrichaceae*), suggesting that these changes could
160 contribute to disease progression and severity [54].

161 From a theoretical point of view, an abnormal microbiota composition characterized by a high
162 abundance of proinflammatory bacteria and low abundance of anti-inflammatory bacteria may
163 generate a systemic inflammatory response through a defective (i.e., “leaky”) gut barrier. This
164 inflammatory response may, in turn, impair the blood-brain barrier, promote neuro-inflammation,
165 and contribute to the pathogenesis of AD [49, 50]. The fecal transplantation from transgenic mice
166 with dementia to cognitively healthy mice induced a worsening of cognitive abilities [55],
167 suggesting a correlation between the gut microbiota composition and cognitive dysfunction.

168 Similarly, studies based on *Drosophila* models of dementia [56] and mouse models of stroke [57,
169 58] showed an association between gut microbiota dysbiosis, cognitive functions and clinical course
170 of the disease.

171 Supporting this view, animal studies have also shown that substances that are able to modify
172 microbiota composition, such as antibiotic agents or probiotics, can modulate inflammatory
173 responses and positively or negatively affect the progression of the disease. For example, long-term
174 antibiotic treatment induced perturbation in gut microbial diversity and altered peripherally
175 circulating cytokine/chemokine composition in APP transgenic mice [59]. This was associated with
176 a reduction in amyloid plaque deposition and elevated levels of soluble β -amyloid, reduced plaque-
177 localized gliosis, and altered microglial morphology [59]. In other experimental studies, antibiotic-
178 induced gut dybiosis was instead associated with increased systemic inflammation and poorer
179 cognitive performance in mice [60, 61].

180 Likewise, gut microbiota manipulation induced by administration of probiotics belonging to
181 *Bifidobacterium* spp. [62-65] or *Lactobacillus* spp. [62, 63, 66, 67] in transgenic mouse models of
182 AD resulted in improved cognitive performance and reduced markers of inflammation and
183 neuropathology. For example, in one of these studies four-week treatment with a probiotic
184 formulation (i.e., SLAB51, a mixture of lactic acid bacteria and bifidobacteria) in the early stage of

185 the disease led to an increase in the abundance of anti-inflammatory *Bifidobacterium* spp. and a
186 reduction in the abundance of proinflammatory *Campylobacteriales* [62]. These changes in
187 microbiota composition were associated with a reduction in the levels of proinflammatory cytokines
188 and a less severe cognitive decline, due to a reduction in brain damage and reduced accumulation of
189 β -amyloid aggregates [62]. Moreover, this probiotic regimen caused a reduction of oxidative stress,
190 another important element involved in the pathogenesis of AD [62].

191 Few studies also demonstrated that the manipulation of the gut microbiota of mouse models of AD
192 through administration of functional foods, like fructooligosaccharides, flavonoids or tea saponins
193 resulted in improved cognitive functions [67-70].

194 Despite this body of evidence, it must be remembered that the results of animal studies may not be
195 immediately transferrable to human beings. Moreover, microbiota-gut-brain communications are
196 bidirectional and the possibility that any changes observed in the microbiota are secondary should
197 be always considered. For example, the activity of the hypothalamic–pituitary–adrenocortical axis
198 and the sympathetic nervous system may be increased in AD, thereby influencing top-down
199 signaling to the gastrointestinal tract [71, 72]. Therefore, activation of these neuroendocrine stress
200 response systems may contribute to the change of microbiota profile, both directly via host-enteric
201 microbiota signaling and indirectly via changes in the intestinal milieu [73].

202

203 **3. The gut microbiota in Alzheimer's disease: human studies**

204 In the last decade, several studies have investigated the correlations between the fecal microbiome
205 and presence of acute or chronic illness [74-76]. Notably, several microbial taxa of the intestinal
206 microbiota play a crucial role in maintaining host homeostasis by modulating immunological,
207 nutritional, metabolic, and physiological functionalities, from infancy to senescence [77-80]. The
208 alteration of this symbiotic homeostasis may be involved in the onset and progression of diseases,
209 not involving only the gastrointestinal system [77-80]. This concept also applies to CNS pathology
210 [81]. Remarkably, the human intestinal microbiota can influence cognitive function, and intestinal
211 bacteria may be involved in the pathophysiology of neurodegenerative disorders, including multiple
212 sclerosis, Parkinson's disease, and of course AD [81].

213 Several studies, mainly conducted with metagenomics sequencing of fecal samples, have explored
214 the possible role of gut microbiota in the pathogenesis of dementia, particularly of AD, highlighting
215 alteration in the intestinal microbial composition of patients in comparison with controls [82-89].
216 The findings of these studies are summarized in Table 1.

217 As highlighted by Vogt and colleagues [83], one of the main differences in the gut microbiota
218 composition, determined through the use of 16S rRNA gene profiling approach, between AD
219 patients and controls is represented by reduced bacterial richness and diversity in subjects with
220 dementia. Moreover, a distinct bacterial profile seems to characterize the gut microbiota of AD
221 patients, who display high abundance of species belonging to Bacteroidetes phylum, such as
222 *Bacteroides* spp. and *Alistipes* spp., and reduced representation of members of the *Bifidobacterium*
223 genus and taxa belonging to Actinobacteria, and Firmicutes phyla [83, 84, 89].

224 Remarkably, overrepresentation of *Bacteroides fragilis* in the microbiota has been associated with
225 the development of AD, probably due to its production of lipopolysaccharide, which could
226 contribute to systemic inflammation [90]. Two studies from China also show increased
227 representation of bifidobacteria in fecal samples of patients with AD, suggesting that this genus
228 may represent a microbial marker of AD [88, 89]. However, bifidobacteria were underrepresented

229 in the fecal microbiota of patients with AD in the Vogt study [83], and the genus *Bifidobacterium* is
 230 generally associated with longevity and healthy aging [91].
 231 In one study, the gut microbiota of AD patients was also characterized by low abundance of
 232 butyrate-producing taxa, such as members of the *Butyrivibrio*, *Eubacterium*, *Roseburia*, and
 233 *Faecalibacterium* genera [86]. Furthermore, deep metabolomic investigations based on microbiome
 234 data of AD patients compared to individuals without dementia highlighted a decrease in butyrate-
 235 coding genes in AD disease [86]. These findings might suggest that lower proportions of butyrate-
 236 producing species would contribute to the onset of the disease.
 237 Moreover, AD patients displayed a tendency towards increase in relative abundance of bacterial
 238 species related to human diseases or able to act as opportunistic pathogens, like *Klebsiella*
 239 *pneumoniae*, *Bacteroides fragilis*, and *Eggerthella lenta* [48, 83, 86, 88, 92]. These species could be
 240 characteristic of a pro-inflammatory microbiota, which might contribute to the pathophysiology of
 241 AD.
 242 Oddly, Emery et al. explored the bacterial load of frozen and fixed post-mortem tissue from AD and
 243 control temporal cortex [93]. This study reported that AD brains tend to have higher bacterial load
 244 than controls, reinforcing the notion of a possible correlation between human gut microbiota and the
 245 development of AD [93].
 246 Two recent systematic reviews and meta-analysis have considered the human studies where
 247 cognitive function was measured as one of the clinical endpoints after administration of probiotics
 248 or prebiotics to subjects suffering from dementia or MCI [94, 95]. The large majority of these
 249 studies were of poor methodological quality, with small sample size, absence of randomization of
 250 treatments and, sometimes, absence of a control group receiving standard of care treatment [94, 95].
 251 Only five studies, with an overall number of 297 participants, had a randomized controlled design
 252 and sufficient methodological quality [96-100]. These studies showed improvement in cognitive
 253 function of participants after probiotic administration, mainly consisting in blends of bifidobacteria

254 and lactobacilli, supporting the existence of a gut-brain axis also in human beings with AD [94-
255 100].

256 However, the clinical significance of these findings, and their impact on the future management of
257 AD is still unknown. More importantly, none of these studies conducted on human beings
258 considered diet as a confounding variable or as a possible modulator of gut microbiota composition.
259

260 **4. Polyphenols and gut microbiota in Alzheimer's disease**

261 *4.1. Overview of polyphenols and their gut metabolites*

262 The consumption of foods rich in polyphenols has been associated with numerous beneficial effects
263 on the risk and development different neurodegenerative diseases [101]. Among polyphenols,
264 positive findings have been highlighted for chlorogenic acids (mostly present in coffee, leafy
265 vegetables and berries), curcumin (mainly present in turmeric) and resveratrol (a stilbene present in
266 grapes and wine) [102], but the most robust evidence is related to flavonoids, the most abundant
267 subclass of polyphenols [103].

268 Two recent surveys conducted on US adult cohorts “The Nurses’ Health Study”, “The Health
269 Professionals Follow-up Study” [104] and “Framingham Offspring Cohort” [105] confirmed that
270 the long-term intake of flavonoids significantly decreased the risks of developing AD and related
271 dementias and subjective cognitive decline markers. Among flavonoid subclasses, the most positive
272 findings on cognitive health have been found for flavones, flavonols, and anthocyanins [102, 105].
273 In another survey, based on 921 older subjects from the US, the authors extrapolated intake data for
274 single phenolic compounds, observing that high dietary flavonol intake, and particularly of
275 kaempferol and isorhamnetin, may be protective against the development of AD [106].

276 Despite the *in vitro* experimental findings of the last decades confirm these molecular mechanisms,
277 one should not forget the complexity of human physiology and, in particular, of the digestive
278 system, and the now proven extensive catabolism of polyphenols in the lower gastro-intestinal tract
279 has induced scientists to re-think what the real biological effectors might be. In fact, once ingested,
280 the polyphenols present *in planta* pass through the oral cavity and stomach almost unmetabolized.
281 Once in the small intestine, only a small amount is absorbed and able to reach the liver and,
282 subsequently, the systemic circulation [107]. The most relevant fraction of ingested polyphenols
283 reaches the colon and undergoes substantial modifications of the parent chemical structures through
284 the action of bacterial enzymes. Thus, most of the biological effects of (poly)phenols are mediated

285 by the intestinal microbiota. The generated bacterial metabolites are then absorbed and may
286 undergo hepatic phase I and, most prominently, II metabolisms [108].
287 The result of such biochemical transformation is the release in the bloodstream of smaller phenolic
288 compounds, including benzene diols and triols, benzaldehydes, benzoic acids, phenylacetic acids,
289 phenylpropanoic acids, cinnamic acids, hippuric acids, and many other compounds, which might
290 sometimes be very specifically linked to their parent phenolic structure [109]. For this reason, in the
291 most recent years, the studies focusing on the role of (poly)phenols on health outcomes are
292 considering, as real biological effectors, the colonic metabolites rather than the compounds that are
293 naturally present in the food source. A recent review by Carregosa and collaborators [109]
294 summarized in a very exhaustive manner the role of the several metabolites, categorized for the
295 single deriving subclasses of flavonoids, on several markers of neurodegenerative diseases, among
296 which AD, tested in very different model organisms, from fungi to humans.

297

298 4.2. Flavan-3-ols

299 Flavan-3-ols are among the most representative contributors of the flavonoid intake in several
300 European countries [110-112]. A recent review from our group comprehensively described the
301 possible colonic metabolites following flavan-3-ol ingestion, showing that phenyl- γ -valerolactones,
302 phenylvaleric acids, and their glucuronide, sulfate and methylated forms are the most abundant in
303 humans [113]. In a study using different *in vivo* animal models, Angelino et al. [114] also
304 demonstrated that one of these metabolites, namely 5-(hydroxyphenyl)- γ -valerolactone-sulfate (3',4'
305 isomer), was effectively detected in brain tissues of the different animals used. Concerning the
306 biological activity, recently our group evaluated the role of such metabolites in counteracting the
307 formation of Amyloid- β oligomers (A β O) in yeast, mammalian cell and mouse models, at
308 physiological concentrations [115]. Results showed that 5-(4'-hydroxyphenyl)- γ -valerolactone was
309 able to counteract the toxicity induced by the formation of oligomers, but not fibrils [115]. The

310 mouse model, characterized by individuals with A β O-induced memory impairment, showed a
311 relieve of the brain tissue morphology and an improvement of the memory functions when the
312 animals were co-exposed to the metabolite [115]. The same compound, as well as 5-(3',4'-
313 hydroxyphenyl)- γ -valerolactone and 5-(3'-hydroxyphenyl)- γ -valerolactone-4'-sulfate, tested up to 5
314 μ M, was effective in modulating cellular proteolysis via proteasome inhibition and consequent
315 autophagy upregulation, together with the inhibition of cathepsin B activity [116]. This led to the
316 decrease of the amount of intra- and extracellular A β_{1-42} peptides.

317 Two recent studies aimed at investigating the amelioration from the A β O toxicity by using extracts
318 rich in flavan-3-ols in cell culture models, and confirmed the presence of flavan-3-ol metabolites in
319 murine models [116, 117]. Another study evaluated the role of a lotus extract (*Nelumbo nucifera*) in
320 the reduction of cellular deformation and apoptosis rate in cells pre-incubated with A β_{25-35} by
321 affecting different cascades involving brain-derived neurotrophic factor (BDNF), phosphorylation
322 of cAMP-responsive element-binding (CREB), protein kinase B (also known as AKT), and the
323 extracellular signal-regulated kinase (ERK) [116]. Authors evaluated the bioavailability of the
324 extract by feeding rats with a 200 mg/kg dose of extract for two days, and confirmed the
325 presence of small phenolic acids, mainly caffeic, vanillic and *p*-hydroxyphenylacetic acids (no
326 conjugated metabolites were measured as β -glucuronidase/sulfatase enzymes were used before
327 analysis) [116]. Similarly, a study in the US demonstrated that different concentrations of a pine
328 bark extract, rich in proanthocyanidins and (epi)catechin, was able to block the formation of
329 aggregates of A β O and *tau* protein [117]. Authors studied the bioavailability of the extract by
330 feeding rats with 200 mg/kg pine bark extract for ten days, identifying in plasma and
331 brain tissues the methylated and glucuronidated conjugates of catechin and epicatechin [117].

332 Concerning human studies, Desideri et al. supplemented with increasing concentrations of cocoa
333 flavan-3-ols, up to 990 mg/day for 8 weeks, older subjects with cognitive impairment, and showed a
334 significant amelioration of the cognitive functions of participants consuming high doses of flavan-3-
335 ols [118]. Moreover, Brickman et al. used the functional magnetic resonance imaging technique to

336 demonstrate that healthy active older subjects consuming cocoa flavan-3-ols (900 mg/day) had an
337 improvement of the cerebral blood flow in the body of the hippocampal circuit, primarily to the
338 dentate gyrus and subiculum, driver of the age-related cognitive decline [119].
339 Different projects are now running to improve our knowledge of the role of (poly)phenol-rich foods
340 on cognitive parameters. Among these, the “Cognitive Ageing, Nutrition and Neurogenesis
341 (CANN)” trial is evaluating the effects of the supplementation of long-chain ω -3 polyunsaturated
342 fatty acids plus 500/day of cocoa flavan-3-ols, for 12 months, on cognitive markers in older subjects
343 from the UK and Australia with mild cognitive or subjective memory impairments [120]. The
344 “Valerolactones and healthy Ageing: Linking Dietary factors, nutrient biomarkers, metabolic status
345 and inflammation with cognition in older adults (VALID)” project aims to demonstrate the validity
346 of the phenyl- γ -valerolactones as biomarker of flavan-3-ol intake and to investigate whether the
347 consumption of foods and beverages rich in flavan-3-ols – and so the presence of specific colonic
348 metabolites – may have a role in the preservation of the cognitive health in the Irish TUDA elderly
349 cohort participants [121].

350

351 4.3. Ellagitannins

352 Pomegranate (*Punica granatum L.*) is a rich source of ellagitannins, a class of condensed tannins
353 which are very poorly absorbed and, instead, reach the colon where colonic bacteria metabolize
354 them to form a group of compounds named urolithins [108]. Pomegranate has been supplemented in
355 different animal studies to evaluate putative biological effects on AD and more general cognitive
356 markers. A Brazilian study revealed that the supplementation of pomegranate peel extract (800
357 mg/kg/die) for 35 days to mice infused with A β O was able to decrease amyloid plaque density and
358 the expression of several brain inflammatory features, other than improving animal behavior,
359 compared to control mice [122]. While in the latter study there is no focus on the colonic
360 metabolites, Kujawska et al. identified quantifiable amounts of urolithin A in brain tissue of rats
361 treated with rotenone to induce cognitive impairment and after the administration of pomegranate

juice (500 mg/kg/die) for 35 days [123]. The authors demonstrated that the pomegranate juice supplementation – and putatively the presence of the microbial metabolite urolithin A – was able to decrease the expression of different oxidative, neuroinflammatory and apoptotic markers [123]. The effect of single urolithins has been investigated both *in vitro* and through animal studies. DaSilva and collaborators evaluated the modulation of inflammation by urolithin A, B and their methylated forms, up to 10 μ M, in single LPS-stimulated microglia cells or in co-culture with neuroblastoma cells [124]. Results showed that all the compounds were able to reduce some neuroinflammatory mediators, like nitric oxide, interleukins, prostaglandins, and pro-apoptotic factors, compared to control. Finally, Gong and colleagues supplemented transgenic AD mouse models with 300 mg/kg urolithin A for 14 days and found an attenuation of neuron death through the inhibition of A β O deposition and a trigger of neurogenesis via inhibition of several markers of neuroinflammation and apoptosis [125].

4.4. Anthocyanins

Anthocyanins are the main contributors to the red/purple color of fruit and vegetables and include compounds such pelargonidin, cyanidin, delphinidin, peonidin, petunidin and malvidin and their glycoside conjugates. Their main colonic metabolites are small phenolic acids, as protocatechuic, gallic, vanillic, syringic and hydroxybenzoic acids [108]. A recent and exhaustive review pointed out that the main metabolites showing *in vitro* neuroprotective effects were protocatechuic, gallic, vanillic acids, limited for other phenolic acids [126]. The most important target of these phenolic metabolites, mostly protocatechuic and vanillic acids, were the antioxidant activities at intracellular level, so counteracting the depletion of glutathione and catalase activities due to peroxide stimulation or improving cell viability after nitro-radical increase in the cell [127, 128]. Not only antioxidant, i.e. superoxide dismutase or catalase, but also inflammation enzymes, i.e. cyclooxygenases, were also inhibited by gallic acid treatment of neuronal cells – despite in high concentrations –, with consequent decrease of cytokine production [129].

388 Concerning immortalized cells, several studies pointed out that gallic, vanillic, and hydroxybenzoic
389 acids are able to block the oligomerization of A β , destabilize pre-fibril and fibril formation, by
390 structural interaction, by metal ion chelation, or by decreasing neuro-inflammatory and apoptotic
391 mediators [130-132]. These findings have been also confirmed in numerous animal models, with an
392 improving of the endogenous antioxidant enzyme activities, as well as the reduction of the presence
393 of several pro-inflammatory cytokines, such as TNF- α , IL-1 β , IL-6, and IL-8, at brain level, by
394 vanillic, gallic and protocatechuic acids [126].

395

396 4.5. Flavanones

397 Flavanones are a flavonoid subclass mainly found in citrus fruits, and the most recurrent aglycones
398 are hesperetin, naringenin, eriodictyol, isosakuranetin and taxifolin, even if the major amounts of
399 them are present as glycoside conjugated [133]. Several studies confirmed a low bioavailability of
400 such compounds, with the identification and quantification of several colonic metabolites in
401 biological fluids, such as phenylpropionic, phenylacetic, benzoic, and hydroxycarboxylic acids and
402 benzenetriol and benzoylglycine derivatives [134]. By considering blood oranges, mandarins, lime
403 and lemon juice, the most representative compound in terms of amount in such fruits is hesperidin,
404 which is the rutinoside of the hesperitin [133]. Hesperidin has been the object of several *in vitro* and
405 *in vivo* animal studies to investigate its role as neuroprotective compound. Concerning AD, the main
406 results have been reported for hesperidin role in counteracting the oxidative stress at neuronal level,
407 with improvement of the antioxidant endogenous mechanisms, such as counteracting glutathione
408 depletion, and decrease of malondialdehyde and H₂O₂ accumulation, other than inhibiting some
409 protein kinase phosphorylation leading to oxidative damage, in animal studies [135, 136].
410 Hesperidin at 100 mg/kg orally administered per 60 days was also found to be effective in the
411 attenuation of the expression of A β precursors and oligomers in rats after aluminum chloride
412 injection to mime the Alzheimer's diseases damages [137]. Several other molecular patterns
413 involved in the boosting of the neuroinflammation have been reduced in a mouse model affected by

414 cognitive impairment when 100 and 200 mg/kg hesperidin has been supplemented for 15 days
415 [138]. Anti-inflammatory and fibril anti-aggregative effects have also been observed in a recent
416 study, where human neuroblastoma cells were incubated with up to 50 μ M liquiritigenin, mainly
417 found in licorice [139]. To date, no human studies have considered the putative biological effects of
418 the flavanones or their colonic metabolites on pathophysiological and clinical markers of AD, and
419 this represents a promising area for future research.

420

421 4.6. Isoflavones

422 Among the so called “phytoestrogens”, isoflavones are a class of compounds mainly found in soy
423 and its derivatives, genistein, daidzein, glycitein, formononetin and their glycosides being the most
424 representative compounds [108]. Studies on urine samples revealed a scarce bioavailability of such
425 compounds, which are mainly metabolized by colonic bacteria in smaller compounds, such as
426 equol, *O*-desmethylangolesin and its 6'-hydroxylated form, which leads to 2-(4'-
427 Hydroxyphenyl)propionic acid, and their conjugates [108]. There is solid evidence of
428 neuroprotective effects of soy and soy-derived foods on several cognitive outcomes in animals and
429 humans [140, 141]. Additionally, AD has been targeted in for studies focusing on isoflavones and,
430 as previously detailed, the most relevant mechanisms highlighted in cell and animal models has
431 been the counteraction of the $A\beta$ deposition, oxidative damage, neuro-inflammation and apoptosis
432 processes [142].

433 However, very few studies considered the colonic metabolites as real biological effectors towards
434 the above-mentioned effects on the nervous system. In a randomized controlled trial, the
435 administration of 100 mg/day of soy isoflavones to 65 older patients suffering from AD did not
436 result in any significant improvement of cognitive function or dementia biomarkers after six months
437 [143]. Researchers correctly argued that not all the individuals are equol-producers, mainly due to
438 the gut microbiota composition and functionality, and so the missing effects of the isoflavone
439 supplementation might be biased by the lack of consideration of this fact in the study design [143,

144]. Actually, when equol was administered to fifteen women with AD, the oxidative and inflammatory markers failed to be effectively modulated, but, clearly, further studies are needed to better understand this interesting aspect [145].

4.7. Flavonols

Flavonols are among the most ubiquitous polyphenols in fruit and vegetables, and quercetin, kaempferol, isorhamnetin and myricetin are the principal representative aglycones, mainly conjugated in several different combinations with one or more sugar molecules [108]. Until recently, the major focus in biological fluids have been aglycones conjugated with glucuronide and/or sulfate moieties, mainly formed during the II detoxification at the upper gastro-intestinal and liver level. However, the simple fermentation of some compounds, such as quercetin, with fecal samples of healthy donors, revealed a deep rearrangement of its chemical structure, leading to the release of smaller phenolic acids, as phenylpropanoic, phenylacetic and hydroxybenzoic acids [146]. A huge load of literature has been published regarding flavonols, and particularly quercetin, involvement in the processes leading to AD and, generally, cognitive disorders [147-148]. Results confirm a role of such compounds in the amelioration of oxidative status at neuronal level, inhibition of inflammatory and apoptotic key pathways, as well as $A\beta$ oligomerization and deposition [147-149]. Also, for this class of compounds, colonic metabolites have not been deeply studied for their putative effects on cognitive decline markers.

4.8. Flavones

Regarding flavones, a flavonoid subclass widely present in vegetable-derived foods and beverages, the most studied compounds are apigenin and luteolin, which are usually present in foods as glycosides, which are barely absorbed along the small and large intestine and, above all, colonic bacteria seem to be unable to cleave the C-linked sugar moiety [108]. However, some data on

465 protective effects of the *in planta* compounds towards AD-related markers, in cell and animal
466 studies, have been reported for apigenin [150] and luteolin [151].

467

468 4.9 Gut microbiota involvement in polyphenol metabolism

469 As previously stated, the catabolism of phenolic compounds in the lower gastrointestinal tract is
470 strictly dependent on the presence of certain bacteria strains, able to vastly modify the parent
471 structures giving origin to smaller phenolic acids that are, in turn, absorbed quite efficiently. In a
472 recent review, Cortés-Martín and collaborators summarized that, despite the many microbiological
473 studies present in the literature, most of the microbial species responsible for specific metabolite
474 production are still unidentified [152].

475 The hydrolysis of the sugar, in the case of the glycosylated polyphenols, is carried out by different
476 species of *Lactobacillus*, *Bifidobacterium* and *Enterococcus*, characterized by the activities of
477 enzymes like glucosidases and rhamnosidases, able to cleave the *O*-sugar moiety (e.g. *Lactobacillus*
478 *plantarum* or *Bifidobacterium pseudocatenulatum*) and, with a lower affinity, C-linkages (e.g.
479 *Enterococcus* spp., *Eubacterium cellulosolvens*, and *Lactococcus* spp.) [152].

480 The elucidation of which species are able to cleave flavonoid rings is still open. Peiroten et al.
481 summarized the main findings related to the metabolism of isoflavones by several different bacteria,
482 identifying several species belonging to *Clostridium* and *Eubacterium* genera as able to transform
483 daidzein into *O*-desmethylangolesin, and *Bifidobacterium*, *Eggerthella*, *Lactococcus* and *Slackia*
484 species as able to produce equol from daidzein [153]. A study from Germany identified two species,
485 namely *Eggerthella lenta* and *Flavonifractor plautii*, in human fecal suspension, able to convert (–)-
486 epicatechin and (+)-catechin into phenylpropanoic and phenylvaleric acids as well as to phenyl-γ-
487 valerolactones [154]. Spanish researchers identified different species belonging to the
488 *Eggerthellaceae* family (*Gordonibacter urolithinfaciens* and *Gordonibacter pamelaee*) as able to
489 convert ellagic acid into urolithins A, B and isourolithin A [155, 156].

490

491 *4.10 The inter-individual variability role in the polyphenol gut microbial metabolism*

492 Epidemiological studies have associated the intake of fruit, vegetables and beverages rich in
493 polyphenols with multiple beneficial effects on the human health. However, when intervention
494 studies looked at the real biological effectors and at cause-effect relationships, a huge variability in
495 terms of production/not production and, sometimes, concentrations of polyphenol gut microbial
496 metabolites in fluids and tissues was observed. The inter-individual variability in the gut microbial
497 capacity to produce peculiar profiles of phenolic metabolites seems to be the most important factor
498 to explain the bioavailability of phenolic compounds and, possibly, the biological response to their
499 intake [157]. The term “metabotype” – metabolic phenotype – has been introduced to indicate this
500 characteristic excretion of metabolites after intake of specific dietary compounds [158].
501 Specifically, the new frontiers in this field will be the identification of cluster of individuals
502 showing a metabotype associated with a well profiled gut ecosystem and, in turn, to a specific
503 health status or improvement of health in response to food intake.

504 The definition of a metabotype should primarily include qualitative data, such as absence or
505 presence of specific metabolites, but could also derive from quantitative aspects, i.e. relative ratios
506 of metabolites [158]. The first pioneering studies in this field have been conducted on soy
507 isoflavones, where the excretion of the urinary metabolites equol and *O*-desmethylangolesin have
508 been observed only in certain individuals after soy consumption [159]. Equol producers have been
509 shown to be characterized by more favorable hormonal profiles and by a lower breast cancer risk
510 [160].

511 The research group led by Tomás-Barberán has shown that not only producers and not producers of
512 urolithins, metabolites of dietary ellagitannins, are linked to specific enterotypes, but that producers
513 can be further clusterized in metabotypes that are then associated to different presence of dysbiotic
514 symptoms and also different cardiometabolic risk profiles [161]. Similarly, our group is working on
515 the elucidation of the possible metabotypes following the ingestion of flavan-3-ol rich foods, with
516 the preliminary findings indicating the presence of distinct groups of individuals excreting

517 trihydroxyphenyl- γ -valerolactones, dihydroxyphenyl- γ -valerolactones, and hydroxyphenylpropionic
518 acids [162, 163].
519

520 **5. Dietary fibers, gut microbiota and short-chain fatty acids in Alzheimer's disease**

521 Dietary fibers include plant-based carbohydrates (non-starch polysaccharides, such as cellulose,
522 resistant oligosaccharides, such as inulin, and resistant starch) that cannot be metabolized by human
523 digestive enzymes [164]. Some gut bacteria are however able to metabolize such dietary
524 compounds, generating SCFAs, i.e., acetate, propionate and butyrate, as endproducts [165].

525 Most bacteria able to synthesize SCFAs belong to the *Ruminococcaceae* and *Lachnospiraceae*
526 families [166, 167]. Few bacterial taxa, including *Roseburia* spp. and *Eubacterium rectale*, are able
527 to complete the degradation of fibers to SCFAs alone [166, 167]. More frequently, there are cross-
528 feeding interactions between taxa belonging to the same ecological niche: fibers are degraded to
529 intermediate products by one group of bacteria, and then these products are utilized by SCFA
530 producers [166, 167]. Alternatively, fiber degradation by one strain is essential for stimulating the
531 growth and metabolic activity of a SCFA-producing strain [166]. The most known of these cross-
532 feeding interactions regards *Bifidobacterium* spp. and *Faecalibacterium prausnitzii*, whose
533 butyrate-producing capacity relies on the supply of acetate by bifidobacteria [168, 169].

534 SCFA synthesis by the gut microbiota is strongly influenced by the amount of fibers introduced
535 with diet, that is able to shape the microbiota composition and enhance the SCFA metabolic
536 pathways [170]. A recent population-based study has shown that the consumption of large amounts
537 of fiber-rich plants is associated with increased representation of SCFA-producing genera in fecal
538 microbiota [171]. A similar effect has also been demonstrated in an intervention study specifically
539 focused on older subjects [172]. However, these effects do not necessarily correspond to an increase
540 in SCFA production, due to the complex cross-feeding interactions among bacteria and variable
541 expression of bacterial metabolic pathways [173].

542 Around 90% of SCFAs produced in the gut lumen are absorbed by colonocytes or enter circulation,
543 while the remaining 10% is excreted in feces [166]. SCFAs exert a wide range of physiological
544 functions in the intestine and in human metabolism, which have been extensively reviewed
545 elsewhere [166, 174] and are summarized in Table 2.

546 The studies investigating fecal microbiota composition in patients suffering from AD generally
 547 show a depletion SCFA-producing bacteria in comparison with controls (Table 3), especially taxa
 548 able to synthesize butyrate belonging to *Lachnospiraceae* or *Ruminococcaceae* [82-87]. However,
 549 butyrate producing bacteria can be isolated and cultivated from fecal samples of patients with AD
 550 [175] and a recent study failed to detect a significant difference in the relative abundance of the
 551 main SCFA producers between patients with AD and healthy controls (Table 3) [88]. Interestingly,
 552 a recent analysis of the gut microbiota composition and fecal metabolomics profile of 21 Chinese
 553 patients with AD and 44 controls with normal cognitive function revealed a paradoxical increase of
 554 representation of some SCFA-producing taxa, such as *Ruminococcaceae* and *Faecalibacterium*
 555 *prausnitzii*, in fecal samples from AD patients [89]. In the light of the existing literature, such
 556 findings suggest that the relationship between gut microbiota composition and cognitive
 557 dysfunction may be strongly influenced by external factors that were not considered as possible
 558 confounders, including dietary patterns and fiber intake. Geographical location of study participants
 559 may also represent an important issue: recent data indicate that study location represents the main
 560 factor explaining inter-individual variability in microbiome studies [176, 177].

561 The gut mycobiome (i.e., ensemble of fungal populations symbiotically living with the host in the
 562 gut lumen) could also interact with the intestinal microbiome in patients with AD. A recent study
 563 has shown that reduced representation of SCFA producers, including *Ruminococcus*, *Lachnospira*
 564 and *Roseburia*, is associated with a distinct intestinal mycobiome composition in patients with AD
 565 [178].

566 Overall, this evidence supports the assumption that patients with AD could have reduced SCFA
 567 synthesis in their gut microbiota. However, the descriptive, cross-sectional design of these studies,
 568 and the absence of direct measurement of SCFA levels in feces or other biological samples does not
 569 allow to make any inference on the causal relationship between SCFA depletion and dementia.
 570 Furthermore, none of these studies considered nutritional intake of fibers as covariate.

571 In experimental models of AD, SCFAs exhibit a neuroprotective effect at multiple levels [179].
572 More specifically, they contribute to modulate the microglial cell function, reducing phagocytic
573 activity, secretion of cytotoxins and synthesis of pro-inflammatory cytokines [179, 180]. In
574 experimental conditions, SCFAs also inhibit amyloid- β aggregations, interfering with amyloid
575 plaque formation and enlargement [181]. Interestingly, the brain amyloid load, measured with
576 standardized uptake value ratio versus cerebellum through florbetapir amyloid-positron emission
577 tomography (PET), was negatively correlated with blood butyrate levels in a group of 89 older
578 subjects with different cognitive function, ranging from normal to overt dementia [182].
579 The clinical translation of these findings remains, however, uncertain. To date, studies specifically
580 investigating the effects of increasing fiber intake on cognitive function and risk of dementia are
581 lacking. Most studies were focused on nutritional patterns and frequency of consumption of fruit
582 and vegetables, indicating that there could be an inverse relationship between fiber intake and
583 cognitive performance, especially in those who already suffer from dementia or subjective cognitive
584 complaints [24, 183-185]. Two studies also showed an inverse correlation between a dietary pattern
585 characterized by elevated fiber intake and imaging biomarkers of AD (i.e., 18F-fluorodeoxyglucose
586 uptake on brain PET in one study [186] and white matter hyperintensities module on brain magnetic
587 resonance in another [187]). However, a large study conducted on 162 older subjects did not find
588 any significant correlation between fiber intake and brain A β burden measured with amyloid-PET
589 [188]. Furthermore, none of these studies considered investigation of SCFAs in their experimental
590 design.
591 From a clinical perspective, the possibility of influencing AD pathophysiology through modulation
592 of the intestinal microbiota towards an enhanced production of SCFAs is intriguing. However, very
593 few clinical trials with probiotics or prebiotics have considered cognition as main endpoint [189].
594 Three recent systematic reviews and meta-analyses have shown contradicting results, supporting the
595 plausibility of favorable effects of probiotics or prebiotics on cognition with a low level of evidence

596 [94, 190, 191]. None of the studied interventions were, however, specifically targeted at increasing
597 SCFA production in the gut, and most studies were limited by small sample sizes.
598 Overall, the current evidence supports the concept that increasing dietary fiber intake is associated
599 with favorable effects in the pathophysiology of AD through mediation of the gut microbiota.
600 However, the clinical relevance of this mechanism and its therapeutic potential remains unclear.
601

602 **6. Conclusions and perspectives**

603 The current state of knowledge allows to hypothesize that the intestinal microbiome stands at the
604 crossroads between nutrition and pathophysiology of AD, and that many of the putative beneficial
605 effects of healthy dietary patterns on cognition could be mediated by the gut microbiota (Figure 1).
606 However, there is still a big gap between preclinical and clinical studies in this field. In fact, the
607 influence of nutrition and gut microbiota on the pathophysiology and clinical course of AD has
608 been studied mainly considering each player in a separate way, without integrating nutritional and
609 microbiological investigations. The evidence suggesting favorable effects of gut microbiota-derived
610 metabolites of polyphenols or fibers on markers of AD mostly comes from *in vitro* studies, and its
611 translation in clinical practice is still difficult. As a result, there is a substantial lack of knowledge
612 on how microbiome-centered nutritional interventions can modify cognitive function from a clinical
613 perspective.

614 However, the gut microbiota could become a reasonable target for anti-dementia interventions in
615 the foreseeable future, as suggested by preclinical studies [80, 179]. Nutritional strategies implying
616 an increase in the intake of polyphenols and fibers have a great potential of being effective in
617 slowing down cognitive decline in older individuals, but future studies should also consider the
618 influence of microbiota composition in this putative association. For example, the cognitive benefits
619 of an increase in polyphenol intake could depend on specific metatypes of the gut microbiota and
620 the benefits, in terms of SCFA production, of increasing fiber intake could be influenced by the pre-
621 existing network of strains with capacity of synthesizing butyrate [192, 193].

622 Future studies should also consider the co-occurrence of cognitive decline and physical frailty in
623 older individuals [194]. Interestingly, gut microbiota dysbiosis is increasingly indicated as one of
624 the contributors to the pathophysiology of physical frailty and sarcopenia [195, 196], concurring to
625 define the health trajectory of older individuals [197]. Effective anti-aging microbiome-centered
626 nutritional interventions should thus consider the link between microbiota and both cognitive and

627 physical domains, translating the evidence coming from microbiological and animal studies into
628 clinical practice.
629

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633

634 **CONFLICT OF INTEREST STATEMENT**

635 All authors report no conflict of interest.

636

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1271 **TABLE 1**
1272 Overview of the findings of the main human studies investigating gut microbiota composition in
1273 AD.

Author, year [ref]	Country	Sample size	Age	Key findings in AD patients
Cattaneo et al, 2017 [82]	Italy	40 amyloid-positive with dementia 33 amyloid-negative with dementia 10 healthy controls	71±7 (AD) 68±8 (controls)	Increase of pro-inflammatory taxa, such as <i>Escherichia</i> Decrease of anti-inflammatory taxa, such as <i>E. rectale</i> Correlation between microbiota composition and circulating inflammatory cytokines
Vogt et al, 2017 [83]	US	25 patients with AD 25 age- and sex-matched controls	71±7 (AD) 69±8 (controls)	Reduced species richness and representation of several taxa including <i>Bifidobacterium</i> Correlation between the abundance of these taxa and cerebrospinal fluid markers of amyloid burden
Zhuang et al, 2018 [84]	China	43 patients with AD 43 age- and sex-matched controls	70±9 (AD) 69±9 (controls)	Different microbiota composition with increase in <i>Ruminococcaceae</i> and <i>Lactobacillaceae</i> and decrease in <i>Lachnospiraceae</i>
Liu et al, 2019 [85]	China	33 patients with AD 32 patients with amnesic mild cognitive impairment 32 healthy controls	75±11 (AD) 70±11 (MCI) 77±9 (controls)	Reduced commensal diversity Decreased representation of <i>Lachnospiraceae</i> and <i>Ruminococcaceae</i> Increased representation of <i>Enterobacteriaceae</i> that negatively correlated with cognitive performance
Haran et al, 2020 [86]	US	24 nursing home residents with AD 33 nursing home residents with other types of dementia 51 nursing home residents without dementia	85±8 (AD) 88±8 (other dementia) 83±10 (controls)	Different microbiota composition clusters among groups Increased representation of <i>Bacteroides</i> , <i>Alistipes</i> and <i>Barnesiella</i> , and reduced representation of <i>Lachnoclostridium</i> and butyrate-producing species
Ling et al, 2021 [88]	China	100 patients with AD 71 age- and gender-matched controls	74±9 (AD) 73±8 (controls)	Reduced species richness Decreased representation of eight key genera, including <i>Faecalibacterium</i> and <i>Roseburia</i> Increased representation of <i>Bifidobacterium</i>
Zhou et al, 2021 [89]	China	60 patients with AD (30 with neuropsychiatric symptoms) 32 healthy controls	73±7 (AD) 71±6 (controls)	Reduced species richness Decreased representation of <i>Eubacterium</i> and increased representation of several genera, including <i>Bifidobacterium</i>

				The abundance of several key genera was associated with symptoms and severity of AD
Xi J et al, 2021 [81]	China	21 patients with AD 44 controls with normal cognition	76±10 (AD) 78±6 (controls)	Alteration of representation of 15 key bacterial taxa Increased representation of <i>Faecalibacterium</i> Altered predicted metabolic profile

AD=Alzheimer's Disease; US=United States.

1276 **TABLE 2**
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1278 Proposed physiological functions of short-chain fatty acids produced by gut microbiota in human
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Actions on gastrointestinal function	<ul style="list-style-type: none"> - Increased expression of tight junctions - Reduced intestinal permeability - Increased mucus production - Improved mucus quality (glycosylation of mucins) - Energetic supply to colonocytes - Modulation of colonic motility - Possible increase of calcium absorption
Actions on gut mucosal immunity	<ul style="list-style-type: none"> - Modulation of mucosal inflammation - Reduction of synthesis of pro-inflammatory cytokines - Modulation of dendritic cell function - Reduction of oxidative stress by enhanced glutathione function - Inhibition of the expression of chemokines and cytokines induced by lipopolysaccharide - Promotion of conversion of naïve T-cells into FoxP3⁺ T_{reg} cells - Stimulation of IgA production (mediated by retinoic acid synthesis) - Induction of expression of antibacterial peptides (cathelicidins)
Actions on the host metabolism	<ul style="list-style-type: none"> - Modulation of body weight (butyrate) or increase in body weight (acetate) - Increased satiety and reduced energy intake - Increased energy expenditure, thermogenesis and basal metabolic rate - Stimulation of lipid oxidation - Decreased circulating fatty acid levels - Stimulation of lipolysis - Stimulation of gluconeogenesis - Decreased fasting glucose levels - Improved insulin sensitivity - Modulation of insulin secretion
Actions on systemic inflammation	<ul style="list-style-type: none"> - Modulation of chronic release of pro-inflammatory cytokines (IL-6, IL-1β, TNFα) - Modulation of adipokine secretion - Reduction of eicosanoid production - Increased neutrophil apoptosis

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TABLE 3

Overview of the findings of studies that have investigated the potential of SCFA synthesis of the intestinal microbiota in patients with AD or other forms of dementia.

Author, year [ref]	Country	Sample size	SCFA-producing taxa depleted in AD	Other key findings
Cattaneo et al, 2017 [82]	Italy	40 amyloid-positive with dementia 33 amyloid-negative with dementia 10 healthy controls	<i>Eubacterium rectale</i>	The abundance of <i>E.rectale</i> was inversely related to brain amyloid deposition
Vogt et al, 2017 [83]	US	25 patients with AD 25 age- and sex-matched controls	<i>Ruminococcaceae</i> <i>Bifidobacterium</i>	Correlations between the abundance of bacterial taxa and markers of neural inflammation
Zhuang et al, 2018 [84]	China	43 patients with AD 43 age- and sex-matched controls	<i>Lachnospiraceae</i>	The abundance of <i>Ruminococcaceae</i> was overall increased in AD subjects
Liu et al, 2019 [85]	China	33 patients with AD 32 patients with amnesic mild cognitive impairment 32 healthy controls	<i>Ruminococcaceae</i> <i>Ruminococcus</i> spp	The abundance of <i>Enterobacteriaceae</i> was the key feature distinguishing patients with AD from other categories
Haran et al, 2020 [86]	US	24 nursing home residents with AD 33 nursing home residents with other types of dementia 51 nursing home residents without dementia	<i>Eubacterium</i> <i>Roseburia</i> <i>Lachnoclostridium</i> <i>Butyrivibrio</i> <i>Faecalibacterium</i>	Depletion of taxa with the potential of synthesizing butyrate is distinctive of AD in comparison with other categories
Ling et al, 2021 [87]	China	100 patients with AD 71 age- and gender-matched controls	<i>Roseburia</i> <i>Faecalibacterium</i> <i>Butyricicoccus</i>	The abundance of SCFA producers inversely correlated with parameters of cognitive function and functional performance
Zhou et al, 2021 [88]	China	60 patients with AD (30 with neuropsychiatric symptoms) 32 healthy controls	None	The composition of microbiota of AD patients was significantly different than controls, but the abundance of the main SCFA-producing taxa was not different.
Xi J et al, 2021 [89]	China	21 patients with AD 44 controls with normal cognition	None	The abundance of <i>Ruminococcaceae</i> and <i>Faecalibacterium</i> was

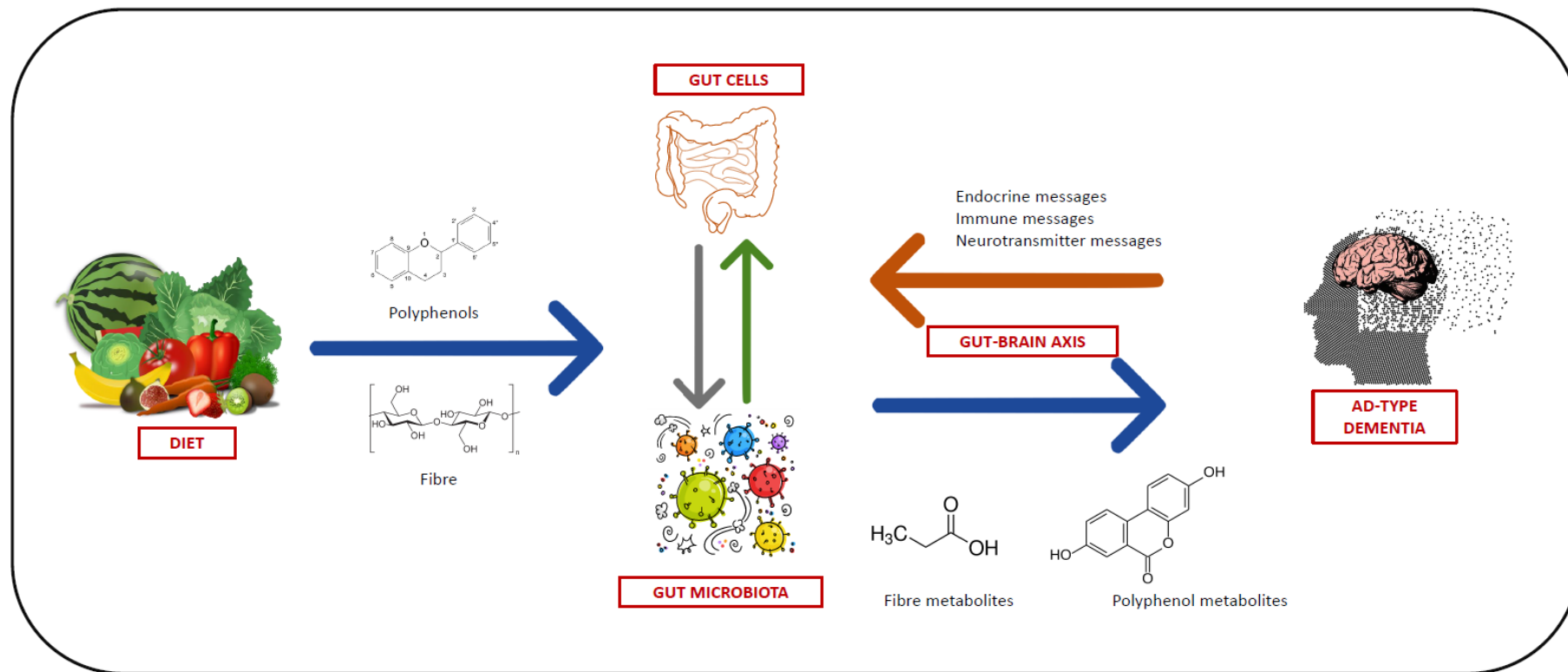
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				increased, and not depleted, in AD patients.
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AD=Alzheimer’s Disease; US=United States

1289 **FIGURE 1**

1290 Overview of the possible link between dietary fiber and polyphenol intake, gut microbiota and modulation of the pathophysiology of Alzheimer's
 1291 disease.
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