

Journal Pre-proof



Exploring Nutraceutical Approaches Linking Metabolic Syndrome and Cognitive Impairment

Rebecca Sonnino, Gea Ciccarelli, Simona Moffa, Laura Soldovieri, Gianfranco Di Giuseppe, Michela Brunetti, Francesca Cinti, Eleonora Di Piazza, Antonio Gasbarrini, Enrico C. Nista, Alfredo Pontecorvi, Andrea Giaccari, Teresa Mezza

PII: S2589-0042(25)00108-7

DOI: <https://doi.org/10.1016/j.isci.2025.111848>

Reference: ISCI 111848

To appear in: *ISCIENCE*

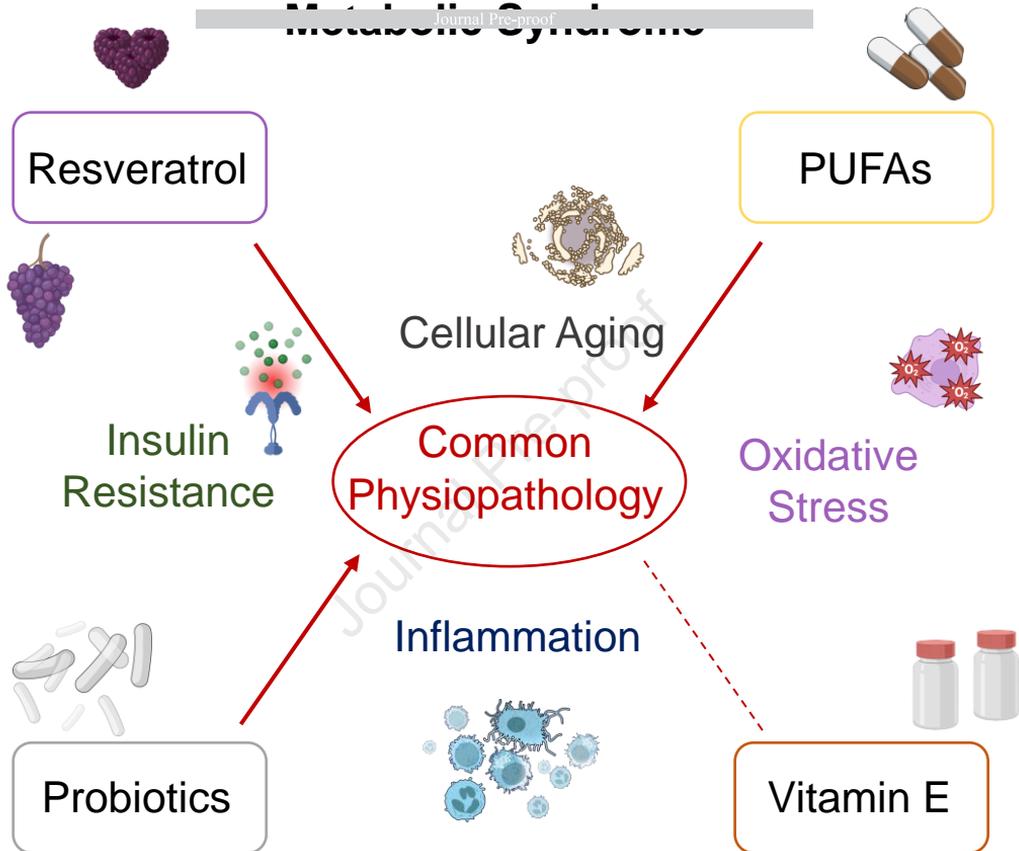
Please cite this article as: Sonnino, R., Ciccarelli, G., Moffa, S., Soldovieri, L., Di Giuseppe, G., Brunetti, M., Cinti, F., Di Piazza, E., Gasbarrini, A., Nista, E.C., Pontecorvi, A., Giaccari, A., Mezza, T., Exploring Nutraceutical Approaches Linking Metabolic Syndrome and Cognitive Impairment, *ISCIENCE* (2025), doi: <https://doi.org/10.1016/j.isci.2025.111848>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2025 Published by Elsevier Inc.

Metabolic Syndrome

Journal Pre-proof



Mild Cognitive Impairment

23 supplementation has emerged as a promising adjunct for the prevention and management of these
24 preclinical conditions.

25 This review examines clinical and translational evidence on commonly used nutraceuticals targeting
26 shared pathophysiological mechanisms of MetS and MCI. By addressing inflammation, oxidative
27 stress, and metabolic dysfunction, these supplements may offer a valuable approach to mitigating
28 the progression and consequences of both conditions. Understanding their efficacy could provide
29 practical tools to complement lifestyle changes, offering a more comprehensive strategy for
30 managing metabolic-cognitive syndrome.

31

32 **Keywords:** metabolic syndrome, mild cognitive impairment, nutraceuticals, inflammation,
33 oxidative stress

34

35 **Glossary**

36 MetS: metabolic syndrome; T2DM: type 2 diabetes; CVD: cardiovascular diseases; MCI: mild
37 cognitive impairment; T3: tocotrienols; TF: tocopherols; AT: adipose tissue; TRF: tocotrienol-rich
38 fraction; AD: Alzheimer's Disease; NGF: nerve growth factor; TG: triglycerides; NAFLD: non-
39 alcoholic fatty liver disease; RSV: Resveratrol; COX-2: cyclooxygenase-2; IL: interleukin; PUFAs:
40 polyunsaturated fatty acids; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; VLC n-3
41 PUFA: very long chain polyunsaturated fatty acids; Nrf2: nuclear erythroid 2-related factor 2;
42 MMSE: Mini-Mental State Examination; TNF- α : tumor necrosis factor alpha; MGB: microbiota-
43 gut-brain axis; hs-CRP: high-sensitivity C-reactive protein; MDA: malondialdehyde; GSH:
44 glutathione; NO: nitric oxide; TAC: total antioxidant capacity.

45

46

47

48

49 **Introduction**

50 Morbidity and mortality due to metabolic syndrome (MetS) make it a global health concern since it
51 is well known that, if left untreated, MetS is strongly associated with increased risk of developing
52 type 2 diabetes (T2DM) and cardiovascular diseases (CVD)^{1, 2}.

53 Poor cognitive function is one of the many adverse health outcomes deriving from MetS. MetS is in
54 fact associated with a higher risk of mild cognitive impairment (MCI) and the progression from
55 MCI to dementia, particularly vascular dementia³ as evidenced by many cross sectional studies and
56 systematic reviews^{4 5 6}. Not surprisingly, an inverse correlation between the presence of MetS and
57 global cognitive performance has often been highlighted^{3 7}, and of all MetS components, high
58 blood pressure and hyperglycaemia seem to be the strongest predictors of impaired cognitive
59 function⁸.

60 One of the most investigated pathogenetic features of metabolic syndrome (MetS) is systemic
61 inflammation also known as "chronic low-grade inflammation," primarily resulting from adipose
62 tissue dysfunction in the context of a high-calorie diet^{9 10 11 12}. This persistent inflammatory state is
63 believed to impact brain function, representing a shared pathological substrate between MetS and
64 MCI^{13 14}. Notably, obesity has been linked to neuroinflammation, initially observed in the
65 hypothalamus and later identified in other brain regions such as the hippocampus, cortex, brainstem,
66 and amygdala. This phenomenon, termed "obesity-derived neuroinflammation," is associated with
67 mood alterations and cognitive decline¹⁵. In parallel with adipose tissue dysfunction,
68 neuroinflammation in the brain has been linked to insulin resistance (IR), defined as reduced
69 cellular sensitivity to insulin¹⁶. More than two decades ago, research demonstrated that the brain is

70 highly responsive to insulin, as evidenced by the presence of insulin receptors on both neurons and
71 glial cells, circulating insulin within the brain, and localized insulin synthesis¹⁷. Subsequent studies
72 revealed a decline in the quantity and activity of insulin receptors in the brain, particularly in aging
73 and Alzheimer's disease (AD) models. This finding has fueled the hypothesis that neuronal insulin
74 resistance may significantly contribute to memory impairment in these conditions^{17 18}.

75 Some authors propose that AD and MCI could be conceptualized as an "insulin resistance brain
76 state"¹. Impaired insulin signaling disrupts critical pathways essential for neuronal health and
77 cognitive function. For example, IR diminishes the activity of the PI3K/Akt pathway, leading to
78 aberrant activation of glycogen synthase kinase-3 beta (GSK3 β). This upregulation promotes tau
79 protein hyperphosphorylation, a hallmark of AD. Furthermore, IR interferes with O-GlcNAcylation,
80 a modification inversely related to phosphorylation, exacerbating tau pathology. Normal insulin
81 signaling also supports the transcription of anti-amyloidogenic proteins such as the insulin-
82 degrading enzyme (IDE) and α -secretase, which reduce amyloid-beta (A β) production. When IR
83 occurs, A β production and aggregation increase, triggering synaptic toxicity. Elevated A β levels
84 further impair insulin signaling, creating a vicious cycle that accelerates cognitive decline¹⁹.

85 Given the strong correlation between cognitive performance and brain insulin resistance,
86 antidiabetic drugs aimed at enhancing insulin signaling have been explored as therapeutic
87 interventions, yielding promising results^{20 21}. Clinical guidelines for diabetes management have
88 increasingly recognized cognitive impairment as a chronic complication of type 2 diabetes mellitus
89 (T2DM), with its incidence being approximately twice as high in individuals with T2DM compared
90 to those without^{22 23}.

91 The primary cause of the interesting overlap between MetS and neurodegenerative disorders is still
92 a matter of debate. However, due to the emerging awareness of this intricate link between metabolic
93 features and cognitive decline, the concept of "metabolic-cognitive syndrome" has recently been

94 introduced indicating a cross-talk between the pathological mechanisms involved in both conditions
95 and their propensity to occur together ⁸ .

96 Hyperglycemia and insulin resistance are known to drive the overproduction of reactive oxygen
97 species (ROS), neuroinflammation, and the disruption of key signaling pathways such as the
98 PI3K/Akt pathway. These changes lead to cellular damage in critical brain regions like the
99 hippocampus and hypothalamus, which play essential roles in cognitive processes, learning, and
100 memory. Alterations in the hippocampus are also linked to deficits in executive functions, such as
101 reduced cognitive flexibility and increased impulsivity. These impairments can hinder effective
102 weight management and adherence to dietary regimens, thus perpetuating the interdependence of
103 mild cognitive impairment (MCI) and metabolic syndrome (MetS) within a complex and self-
104 reinforcing vicious cycle.

105 Conversely, weight loss has been consistently associated with improvements in cognitive functions,
106 including memory and executive control. Supporting this connection, several studies have explored
107 dietary interventions using functional food products, such as *Opuntia ficus-indica* (prickly pear
108 cactus), in animal models of MetS. These studies reported enhanced behavioral performance and
109 overall cognitive improvements. At the biochemical level, such interventions were shown to
110 improve lipid profiles and reduce oxidative stress markers, with concurrent modulation of
111 circulating leptin levels ²⁴. Further evidence from mouse models of MetS-associated cognitive
112 decline highlights the benefits of dietary changes. Specifically, transitioning from a high-fat diet
113 (HFD) to a low-fat diet and administering repeated infusions of plasma from healthy mice to HFD-
114 fed mice have demonstrated notable memory improvements. These findings emphasize the potential
115 of dietary strategies in mitigating cognitive decline linked to MetS ²⁵.

116 As both MetS and MCI are characterized by a slow and discontinuous progression, they represent
117 an intermediate clinical phenotype between a healthy condition and the fully manifest disease.
118 Therefore, both disorders can be seen as a time interval in which it may be possible to intervene and

119 delay progression to dementia²³ or T2DM and CV outcomes¹. Unfortunately, this silent evolution
120 makes the diagnostic work up slower. Moreover, given the inconclusive data available regarding the
121 exact mechanism behind them, there are currently no codified therapies available for treatment or
122 prevention.

123 Certainly though, MetS and MCI are both multifactorial conditions, with environmental and genetic
124 factors contributing to their development. In addition, lifestyle factors, especially lack of physical
125 activity and excessive nutritional intake, have been identified as major contributors¹. Consequently,
126 multidomain lifestyle modifications have been proposed as a valid therapeutic strategy^{9 10 26 27 28}
127 ²⁹. Cardio metabolic risk factors usually develop in middle age, suggesting the importance of
128 preventive approaches for target population in their 40s and 50s. Also, it has been demonstrated that
129 young adulthood and middle age are crucial periods for determining cognitive health in old age³⁰.
130 Modifiable lifestyle factors in the prevention of MCI and dementia are diet, physical activity,
131 cognitive and social engagement, smoking and alcohol consumption. Similarly well-known
132 modifiable lifestyle factors in the prevention of MetS and then T2DM are diet and physical activity.
133 Based on the importance of diet for both conditions and on the urgency of prevention, great interest
134 has risen in the non-pharmacological approach through the use of nutraceuticals^{31 32 33}.
135 Nutraceuticals are a food or part of food capable of providing beneficial health effects, including the
136 prevention and the treatment of diseases³⁴. These products have risen interest in different fields for
137 the fewer side effects and long-term safety along with a broad therapeutic effect. Indeed, the same
138 nutraceutical can address different diseases with common pathways and risk factors, as MCI and
139 MetS.

140 Since MCI and MetS are conditions at risk of evolution in overt non-communicable diseases -
141 T2DM and dementia- and since a recognized pharmaceutical strategy has not been found for any of
142 the two conditions, in this review, we aim to explore data on the nutraceutical approach to MCI and
143 MetS, as a possible alternative to medical treatment and/or as an useful add-on to diet and physical

144 activity. Specifically, we explore the role of different type of nutraceuticals, as vitamins, botanicals,
145 dietary supplements and probiotics, known for their anti-inflammatory and antioxidant properties,
146 that may exert a role in MCI and/or MetS. There is a considerable body of literature on the subject
147 and our selection was guided mostly by the potential role of these compounds in clinical practice.
148 Also, we did not reported literature about well-known and recognized nutraceuticals in the context
149 of MCI and MetS, such as B group vitamins and iron, and, in contrast, we did not reported
150 nutraceuticals that have not been studies in these two conditions so far. We rather focused on
151 elements presenting heterogeneous results in RCTs, highlighting gaps in the literature and possible
152 critical explanations for any controversial finding. In Table 1, we listed the compounds that we have
153 selected, classified according to their properties, i.e. mostly anti-inflammatory, mostly antioxidant
154 or both.

155

156 **The role of vitamin E in MetS**

157 Vitamin E is a fat-soluble vitamin found in seeds, nuts and seed oils. Its components, particularly
158 tocotrienols (T3) and tocopherols (TF), are antioxidants, due to their ability to utilize the free
159 hydroxyl group on the chromanol ring to capture free radicals, resulting in a reduction of the
160 glutathione redox ratio and plasma lipid peroxidation^{35 36}. Due to the latter properties the effects of
161 vitamin E, particularly T3 and TF, on MetS have been investigated in both animal models and
162 human studies with contradictory results³⁷.

163 In obese mouse models, Zhao et al³⁸ have shown that T3 supplementation leads to accumulation of
164 this vitamin in adipose tissue (AT). Mice were fed a high-fat (HF) diet supplemented with 0.05%
165 γ T3 for 4 weeks and showed a lower accumulation of fat depots in liver, epididymis and mesentery
166 than MetS-mice without vitamin E supplementation. Concomitantly, mice supplemented with γ T3
167 also showed lower levels of fasting glucose, insulin and proinflammatory cytokines, improved
168 glucose tolerance and insulin sensitivity. Zhao et al also demonstrated in vitro that T3 may exert a

169 positive role in impaired AT by suppressing M1 macrophage differentiation, reducing inflammation
170 and ultimately improving insulin signaling³⁸. This evidence has been recently confirmed by Kato Y
171³⁹, who demonstrated that treatment with T3 inhibited white adipose tissue accumulation and
172 elevation of serum cholesterol concentrations in HFD mice.

173 Studies in humans have yielded similar positive results: Manzella et al⁴⁰ observed a positive effects
174 of vitamin E (all-rac-alpha-tocopheryl acetate, 600 mg die for 4 months) supplementation on the
175 cardiac autonomic nervous system in subjects with diabetes, showing an increased antioxidant
176 capacity, significantly decreased plasma catecholamine concentrations, HOMA index and HbA1c
177 values. The 4 months length of time was specifically chose by the authors as they considered it the
178 minimum length of time necessary to observe effects of vitamin E supplementation, based on
179 previous groups' studies⁴¹. Considering oxidative stress as a main effector of the unbalanced
180 sympathetic-parasympathetic tone typically expressed in subjects with diabetes, these results may
181 indicate that vitamin E, which lowers oxidative stress, could exert beneficial effects by improving
182 metabolism, downregulating inflammatory mediators and rebalancing autonomic activity. These
183 results in diabetic models appear to be congruent with an effect of vitamin E on oxidative stress
184 induced by glucotoxicity. Interestingly, there is also indirect evidence that this nutrient plays a role
185 in the preservation of beta-cells^{42 43 44}. Indeed, Asayama et al.⁴⁵ found that rats deficient in vitamin
186 E had diminished insulin secretory reserves, implying that vitamin E level can directly influence
187 pancreatic islet function.

188 Vitamin E has also been investigated in hypertension. Supplementation with tocotrienol-rich
189 fraction (TRF) was found to reduce the incidence of pregnancy-induced hypertension^{46 47}. In
190 particular, Aminuddin et al⁴⁷ showed an association between vitamin E (TRF 100mg daily in super
191 olein for a six month period minimum, beginning from 12 to 16 gestational weeks until delivery)
192 supplementation and a reduction in the incidence of preeclampsia and maternal hypertension, after
193 controlling for other confounders such as age and maternal weight (Table 2).

194 Other studies aiming to assess the effect of antioxidant supplementation on hypertension, have
195 found a hypotensive effect^{48 49} Following the same rationale, many RCTs have tried to demonstrate
196 a beneficial effect of vitamin E on hypertension, with conflicting results. Palumbo et al.⁵⁰ explored
197 the effect of vitamin E (300 mg once a day for 12 weeks), on systolic and diastolic blood pressure in
198 treated hypertensive patients. The authors found no clinically relevant effect on blood pressure in
199 hypertensive patients already in treatment. The same results were obtained in a study⁵¹ on 89
200 randomized patients treated with vitamin E 1,800 IU daily or placebo for a 12 month-period (Table
201 2).

202 Despite these contradictory results, vitamin E has proven overall to have a positive impact on the
203 oxidative stress and systemic inflammation generated by metabolic conditions such as MetS.
204 However, more research is required to assess the exact target of this nutraceutical, in order to
205 standardize it as a useful tool for MetS treatment.

206

207 **The role of Vitamin E in MCI**

208 As a correlation has been reported between Alzheimer's Disease (AD) and MCI and lower levels of
209 tocopherol⁵², many studies have investigated the antioxidant properties of vitamin E and its major
210 elements for a possible role in lowering or delaying the process of intellectual deterioration in
211 MCI⁵³ with conflicting results.

212 Studies exploring the role of vitamin E on cognitive impairment in both animal models and human
213 patients^{54 55} found it useful not only for its antioxidant capacity, but also because it has an up- or
214 down-regulating effect on some genes involved in the pathogenesis of neurodegeneration in AD.
215 Indeed, vitamin E deficiency has been shown to induce an increase in cerebellar oxidative stress, as
216 suggested by the high levels of protein nitrosylation found in a *Ttpa*^{-/-} knock-out mouse model⁵⁴.
217 The *Ttpa* gene encodes for a protein responsible for the selective excretion of RRR- α -tocopherol

218 from hepatocytes to circulating lipoproteins that transfer the vitamin to non-hepatic tissues, such as
219 neurological tissue. Subjects carrying loss-of-function mutations in the Ttpa gene develop ataxia
220 associated with extremely low vitamin E levels (less than 2 μM) compared with the normal range of
221 18–36 μM ⁵⁶. Furthermore, a significant expression of Ttp was demonstrated in the brain as well as
222 in the placenta, suggesting that this protein provides additional protection to vulnerable tissues^{54 56}.

223 Moreover, comparing rats receiving a diet without vitamin E with rats fed a standard diet, Rota et al
224⁵⁷ found that the nerve growth factor (NGF), a neurotrophin that promotes neuron survival, is less
225 expressed in rats without vitamin E supplementation, compared with models supplemented with 60
226 mg/kg for a period of 9 months⁵⁷. In contrast, studies investigating the efficacy of vitamin E
227 supplements to treat MCI and AD have found no evidence that this intervention prevents
228 progression of dementia or improves overall cognitive function^{50 56 58}.

229 Some authors³⁵ have explained the contradictory results on the efficacy of vitamin E in improving
230 cognitive function with the interesting concept of “the vitamin E paradox”: in a prospective, double
231 blind, placebo-controlled study with 57 AD subjects, 800 IU of vitamin E supplementation per day
232 for six months led to an acceleration in mental deterioration. Studies have found a possible
233 explanation for these results in identifying two sub populations who react in opposite ways to
234 vitamin E supplementation: subjects in whom vitamin E acts as an antioxidant, respond positively
235 to treatment, especially in terms of prevention of functional decline, while in the other subset of
236 patients, who do not respond to treatment with this vitamin, there is no improvement in oxidant
237 level, with a worsening in cognitive function^{58 59} (Table 2). However, the clinical traits that
238 distinguish the different phenotypes remain as yet unknown.

239

240 **The role of vitamin E in the prevention of MCI/MetS**

241 A limited number of studies have examined the effects of vitamin E on cognitive function in healthy
242 populations, with inconclusive and conflicting results⁶⁰. Maxwell et al⁶¹ using data from the

243 Canadian Study of Health and Aging (CSHA), reported that supplemental use of antioxidant
244 vitamins, including vitamin E, reduced the risk of significant cognitive decline and the incidence of
245 vascular dementia.

246 The prospective Rush Memory and Aging Project⁶² showed an inverse association between levels
247 of γ -tocopherol and amyloid loads along with neurofibrillary tangle pathology. However, the trial
248 failed to provide evidence of a statistical interaction between clinical cognitive impairments and
249 tocopherol levels. On the contrary, the Women's Health Study, with 6,377 women over 65 years,
250 observed no significant effect of long term use of vitamin E on cognitive function⁶³. In a phenytoin-
251 induced cognitive impairment rat model, Nagib MM and colleagues demonstrated that alpha
252 tocopherol supplementation alleviates the cognitive impairment suppressing oxidative damage⁶⁴.
253 Also, in old rats, vitamin E have proved to improve cognitive and motor abilities, through
254 increasing the synthesis rate of monoaminergic neurotransmitters⁶⁵.

255 This finding suggests the possible preventive function of vitamin E on cognitive impairment,
256 however more RCTs with selective use of vitamin E are required to confirm this.

257 Vitamin E has also been investigated for its anti-hyperlipidemic properties, through post-
258 transcriptional mechanisms. In healthy animal models, studies have shown a reduction in
259 cholesterol and a significant effect in decreasing body weight. Furthermore, Qureshi et al⁶⁶ showed
260 efficacy of 50 mg alpha-tocopherol per day for 35 days (compared with lovastatin) in lowering total
261 cholesterol, LDL-C, apoB, triglycerides (TG), glucose, and glucagon levels in an hereditary
262 hypercholesterolemic swine model.

263 Vitamin E has also been reported to have an inverse association with non-alcoholic fatty liver
264 disease (NAFLD) in humans. Qi et al ⁶⁷ conducted a cross-sectional study with data from the
265 National Health and Nutrition Examination Survey (2017–2020), and after adjusting results for
266 confounders, observed that dietary intake of vitamin E had a protective role against NAFLD^{66 68}
267 (Table 2).

268 Kato Y and colleagues⁶⁹ have demonstrated - in HFD mice – that T3 treatment inhibits body weight
269 gain and attenuates brain oxidation. It seems that vitamin E can delay but not arrest the body weight
270 gain associated to an hypercaloric diet and it can prevent brain oxidation via antioxidative effect as
271 well as by upregulating antioxidative defence system⁶⁹. Later, the same group have demonstrated
272 that high fat high sucrose diet in mice decrease their learning ability and that T3 treatment prevent
273 its change⁷⁰. All this evidence show how vitamin E could prevent first steps of obesity-related
274 cognitive impairment.

275 These findings could suggest a potential role of vitamin E in the prevention of MetS, as some
276 studies have highlighted the impact of this nutrient on all syndrome-related comorbidities.

277

278

279 **The role of Resveratrol in MetS**

280 Resveratrol (RSV), known also as 3,5,4V-hydroxystilbene, is a natural polyphenol produced by
281 plants in response to environmental stress⁷¹. As all polyphenols, it derives from phenylalanine and
282 is composed of an aromatic ring with a reactive hydroxyl group⁷². It is a popular nutraceutical,
283 known especially for being responsible for the beneficial health effects of wine, and identified as
284 the main player in the questionable “French paradox”⁷¹. Foods containing this extract, such as
285 cocoa, green tea and wine, are derived from plant sources⁷³.

286 Scientific research has investigated this element for its involvement in various pathways, and
287 specifically for its ability in targeting antioxidant and anti-inflammatory mediators.

288 Due to its pleiotropic effect RSV has a substantial impact on metabolism, as evidenced in animal
289 and human studies. It has been shown to improve glucose homeostasis and insulin secretion,
290 playing a role in the modulation of insulin resistance, and protecting pancreatic beta-cells mainly by

291 upregulating adenosine monophosphate (AMP)-activated protein kinase in various tissues of
292 diabetic subjects⁷⁴.

293 RSV has been shown to improve body fat accumulation and energy balance. In both white and
294 brown adipose tissue it actively decreases lipid accumulation by modulating different pathways
295 resulting in upregulation of lipolysis and reduction of lipogenesis in mature adipocytes⁷⁵⁷⁶.

296 Considering the crucial role played by oxidative stress in the development of vascular dysfunction
297 triggered by hypertension, RSV has been shown to increase endothelial nitric oxide bioavailability
298 by enhancing its transduction pathway. Kim et al⁷⁷ have shown a positive effect of a mixture of
299 resveratrol 40 mg/kg for 6 months on vascular dynamics, and thus on hypertension, through the
300 modulation of the renin-angiotensin system. However, whether RSV has an effect on lowering
301 blood pressure or not, remains debatable⁷⁸.

302 Asgary et al.⁷⁹ carried out a meta-analysis to determine the association between resveratrol intake
303 and metabolic parameters in patients with metabolic syndrome. Results were encouraging and
304 consistent with a positive impact of nutraceuticals on MetS. Out of 16 studies analyzed, (10 on
305 humans and 6 on animal models), supplementation with RSV at the dosage of > 500 mg proved to
306 be effective in increasing HDL levels, and decreasing BMI, TG, and glucose levels⁷⁹ (Table 2).

307 Due to its impact on all MetS domains this nutrient is therefore an excellent candidate for MetS
308 treatment and prevention.

309

310 **The role of RSV on MCI**

311 There is an ample body of literature documenting the beneficial effects of RSV on cognitive
312 decline^{80 81 82 83}. In animal models, RSV treatment improved memory and learning ability compared
313 with controls. Resveratrol also improved net neurogenesis and microvasculature, decreased
314 astrocyte hypertrophy, and microglial activation in the hippocampus, demonstrating an effective

315 neuroprotection⁸¹. In vivo experiments conducted by Gomez et al⁸³ on both normal aging and
316 cognitively impaired animal models, showed that RSV 50 mg/kg/day for 12 weeks could reverse
317 cognitive impairment via inhibition of the production of inflammatory cytokines resulting in an
318 improvement in spatial and emotional learning memory⁸³.

319 The most studied mechanism through which RSV is believed to provide neuroprotection is its
320 ability to reduce some proinflammation pathways, through the inhibition of the cyclooxygenase-2
321 (COX-2), 5-lipoxygenase, and nuclear factor- κ B. It is also associated with the upregulation of
322 interleukin (IL)-10 and the downregulation of interferon- γ and IL-17. Both anti-inflammatory and
323 antioxidant effects of this natural component represent an attractive alternative in the treatment of
324 neurodegenerative diseases⁸⁰. Moreover, it has been shown that in human endothelial cells,
325 resveratrol induced vasorelaxation by stimulation of K-Ca channel⁸⁴ which could be the mechanism
326 responsible for its preventive role in cardiovascular diseases and their consequences.

327 Experimentation with RSV supplementation in normal aging humans has shown ubiquitarian
328 effects. Witte et al⁸⁵ reported that 26 weeks of resveratrol intake (200 mg/d) resulted in
329 improvement of verbal memory performance through an increased functional connectivity of the
330 hippocampus, moreover, subjects in the treatment group showed a significant reduction in HbA1c
331 compared with placebo⁸⁵. This double positive effect was confirmed in MCI human models: a RCT
332 performed on 110 subjects diagnosed with MCI⁸² showed a moderate reduction of HbA1c
333 concentration and preserved left anterior hippocampus volume. These results seem to be in line with
334 the previously demonstrated effect of RSV on cerebral flow. The authors also describe the reduction
335 of glucotoxicity in the brain tissue and the increase in the functional connectivity between the
336 hippocampus and different brain regions as the potential mechanisms underlying the positive
337 influence of RSV on neuroactivity. As reviewed by Buglio et al⁸⁰ literature offers many examples of
338 RCTs showing the benefits of RSV in patients with MCI or AD. Moreover, RSV has been shown to
339 have a preventive effect on AD, reducing amyloid plaques in animal models with AD⁸³(Table 2).

340 These promising results highlight a possible therapeutic strategy for MCI, as there is currently no
341 effective pharmacological intervention for this condition.

342

343 **The role of RSV in the prevention of MCI/MetS**

344 RSV has been reported to play a protective role in hypertension, dyslipidaemia, obesity and insulin
345 resistance. It also been shown to act as an antioxidant and to be neuroprotective by inhibiting the
346 production of inflammatory cytokines^{80 81 86 87}. Therefore, given the possible benefits in a healthy
347 population, including weight loss, rebalanced metabolic function and normal aging, RSV emerges
348 as a promising tool for the prevention of MetS and MCI.

349 In female Senescence Accelerated Mouse-Prone mice, it has been demonstrated that a resveratrol-
350 enriched diet, for two months prior to mating, prevent cognitive impairment in mice offspring
351 through epigenetic changes and cell signalling pathways⁸⁸. Moreover, Wu Z and colleagues⁸⁹ have
352 demonstrated that a resveratrol and selenium rich milk supplementation ameliorates cognitive
353 function in d-galactose-induced cognitive dysfunction model mice⁸⁹.

354 In obese humans, Timmers et al⁹⁰ reported a variety of improvements after treatment with 150 mg
355 per day of RSV for 30 days, including glycemic control and insulin sensitivity, along with a
356 reduction in serum levels of inflammatory markers. Konings et al⁹¹, on the other hand, focused on
357 changes in adipose tissue morphology, showing a reduction in the size of abdominal subcutaneous
358 adipocytes in subjects treated with RSV (150mg per day) for 30 days (Table 2).

359 Regarding its role in MCI prevention, as previously reported, Witte et al⁸⁵ proved its effectiveness
360 in neuroprotection in normal subjects. The study analyzed the effect of 200 mg/d of RSV for 26
361 weeks in twenty-three healthy overweight older patients. Through the assessment of working
362 memory, neuroimaging, serum parameters, anthropometric records, and vascular markers, the
363 authors registered improvements in the integrity and functionality of the hippocampus, along with a
364 reduction in body fat and in HbA1c.

365 Experimental findings have proved RSV to be effective, to some extent, in both metabolism and
366 neuroactivity pathways. Indeed, Gocmez and collaborators have demonstrated that resveratrol
367 supplementation (20 mg/kg/day, ip) for 4 weeks after induction of diabetes by streptozotocin in rat
368 prevented cognitive decline, occurring in diabetes mice without resveratrol supplementation. In
369 particular, their data demonstrated that resveratrol prevents memory deficit, endothelial
370 dysfunction, increased oxidative stress and inflammation in a vascular dementia rat model^{83 92}. A
371 similar result has been shown by Tian and colleagues, who demonstrated that resveratrol
372 supplementation improved neuronal injury and cognitive performance by attenuating oxidative
373 stress and inflammation as well as inhibiting synapse loss in diabetic rats⁹³.

374 Overall, this evidence demonstrated that resveratrol may be useful in MetS and MCI alone, but also
375 to prevent cognitive decline in metabolic disease.

376

377 **The role of PUFAs on MetS**

378 Dietary intake of polyunsaturated fatty acids (PUFAs) and Omega-3-fatty acids has been shown to
379 have positive cardiovascular effects. Major sources of PUFA are tofu, and some nuts and seeds such
380 as walnuts and sunflower seeds, while Omega-3-fatty acids, eicosapentaenoic acid (EPA, 20:5) and
381 docosahexaenoic acid (DHA, 22:6), are mostly found in fish and other seafood. It is well known
382 that dietary patterns enriched with these foods are associated with positive cardiometabolic
383 outcomes⁹⁴ For this reason this supplement is largely used in clinical practice, as Omega-3-fatty
384 acids in particular are the first-line therapy for hypertriglyceridemia^{95 96}.

385 A meta-analysis was run in 2023⁹⁷ on the effects of omega-3 PUFAs on the different features of
386 MetS, such as total lipid profiles, blood pressure, and inflammatory markers. As a result, the authors
387 confirmed a significant reduction in TG levels, with a linear relationship between the duration of
388 omega-3 PUFAs intake and changes in TG. Interestingly, supplementation also had a favourable

389 effect on blood pressure and inflammatory markers such as IL-6, tumor necrosis factor alpha (TNF-
390 α), CRP, and IL-1 levels.

391 A review by Brady et al⁹⁸ on the intake of very long chain polyunsaturated fatty acids (VLC n-3
392 PUFA) in MetS subjects found similar effects on lipid profiles, but no impact on glucose
393 metabolism and insulin action. Regarding the effect on glycaemic metabolism, some studies^{99 100 101}
394 highlighted a worsened glucose control in the intervention group, while others^{93 102} evidenced a
395 protective role. A recent study suggested that use of n-3 PUFAs supplements may significantly
396 decrease serum triglyceride levels and lower blood pressure in patients with MetS. In this study, n-3
397 PUFAs increased insulin sensitivity, leading the authors to hypothesize a role in the prevention of
398 hyperglycaemia¹⁰³ (Table 2).

399

400 **The role of PUFAs on MCI**

401 The composition of the neuronal membrane is believed to be directly affected by diet; this idea has
402 focused attention on the role of PUFA supplementation on brain health¹⁰⁴, including psychological
403 distress¹⁰⁵ and cognitive impairment. PUFAs influence cognitive function through several
404 mechanisms, with effects on brain development, neurotransmission, modulation of ion channels and
405 moreover neuroprotection^{104 106 107}. Additionally, many of these functions are dependent on
406 neuronal membrane fluidity; as rigidity increases during aging, PUFA are believed to be useful in
407 maintaining the proper architecture of the membrane¹⁰⁸.

408 One of the interesting aspects of PUFAs is their ability to modulate the production of inflammatory
409 cytokines¹⁰⁹, which are supposed to be active effectors of neurodegeneration, in different
410 pathological conditions. Data from preclinical studies support the hypothesis that PUFAs can
411 actively interfere with inflammatory pathways involved in neurological weakening by positively
412 regulating the transcription of nuclear erythroid 2-related factor 2 (Nrf2), resulting in an

413 upregulation of antioxidant proteins, and by converting the phenotype of microglial cells from
414 macrophage M1 state to an M2 state¹⁰⁹.

415 Several RCTs^{110 111 112 113} have been conducted with the aim of proving that regular intake of these
416 micronutrients can help the neurological system of subjects with MCI better cope with aging and its
417 inflammatory pattern.

418 Freund Levy et al¹¹⁰ performed a RCT analysing the effect of six-month supplementation of ω -3
419 fatty acids (1.7 g of docosahexaenoic acid and 0.6 g of eicosapentaenoic acid) in patients with mild
420 to moderate AD and found no significant impact as measured using the Mini-Mental State
421 Examination (MMSE) or the cognitive portion of the AD assessment scale. Interestingly, the study
422 of a subgroup of 32 patients with very mild AD (MMSE 27 points) revealed a statistically
423 significant treatment effect in the MMSE scores over time between the 2 groups. The authors
424 concluded that when the disease is clinically advanced, the neuropathological substrate is too
425 developed to be attenuated by anti-inflammatory activity. As shown by this trial, there may be a
426 critical period to halt this process, i.e., 2 years or more before the onset of dementia, during which
427 inflammatory molecules likely mediate cognitive impairment and can be successfully targeted to
428 restore cognitive function.

429 To explore this possibility, Solfrizzi et al¹¹⁴ conducted a prospective study on non-demented elderly
430 subjects to evaluate the role of PUFA supplementation. Their data revealed that only highdose
431 PUFA supplementation showed a borderline, but non-significant, trend for a protective effect
432 against the development of MCI.

433 In subjects with MCI, a 12-month period intervention with fish oil supplementation high in DHA (3
434 soft gelatine capsules each day, each containing 430 mg of DHA and 150 mg of EPA), showed a
435 positive impact on almost every cognitive domain¹¹². This evidence supports the hypothesis that
436 MCI is an intermediate phase in the cognitive decline spectrum, which can be reversed if properly
437 treated. Promising results on cognitive domains have been observed in a cohort of 50 people aged

438 over 65 with MCI randomised to receive a supplement rich in EPA (1.67 g EPA þ 0.16 g DHA/d; n
439 17), DHA (1.55 g DHA þ 0.40 g EPA/d; n 18) or the n-6 PUFA linoleic acid (LA; 2.2 g/d; n 15) for
440 6 months¹¹³, although no significant effect was reported overall on depressive symptoms and quality
441 of life. A meta-analysis by Mazereeuw *et al.*¹¹⁵ also reported a protective effect on certain cognitive
442 domains in MCI subjects after supplementation with n-3 fatty acids.

443 This benefit on selected neuropsychological spheres may be due to targeted modulation of synaptic
444 plasticity in specific brain areas that are particularly susceptible to oxidative stress¹¹⁶.

445 Similar results were obtained in a case control study run in 2013 by Lee *et al.*¹¹⁷ in which PUFA
446 intake was found to be positively correlated with cognitive function in patients with MCI. In this
447 study, lipid peroxidation was used as a biomarker of oxidative damage as it is known to be higher in
448 MCI patients compared with the normal aging population, and was found to be significantly
449 decreased after regular administration of PUFAs compared to the control group (Table 2).

450 These studies do, however, have some limitations, for example, the length of the follow up, limited
451 to up to six months, and the small size of the cohort analyzed. Moreover, considering the countless
452 biological pathways involved in neuronal aging, it is difficult to decide which markers should be
453 selected for this kind of research.

454 Overall, in RCTs, PUFAs have proven to have some influence on neural development, neurological
455 aging, neuroinflammation and neuroprotection in general¹¹⁸, together with a high safety and
456 tolerability profile. Therefore, the introduction of PUFAs supplementation is probably a promising
457 alternative in the management of MCI.

458

459 **The role of PUFAs in the prevention of MCI/MetS**

460 PUFAs interventions in MCI in prediabetic, non-cognitively impaired animal models have shown
461 protective effects on brain health¹¹⁹. In fact, Guo *et al.* showed that brain aging models (induced by

462 D-Gal administration), with metabolism-related disorders, benefited from dietary intake of PUFAs.
463 Neurocognitive tests and biochemical essays to detect metabolism parameters and oxidant activity
464 showed that PUFAs exerted two effects: a reduction in the levels of brain receptor for advanced 14
465 glycation end-product (marker of oxidative stress) and plasma TNF- α , and the attenuation of
466 abnormal metabolic characteristics in the D-gal-treated aging rats¹¹⁹.

467

468 In humans, data from a meta-analysis¹¹⁵ investigating the impact of PUFAs on cognitive health,
469 showed the lack of accountability across these studies due to several biases, such as the short
470 intervention period and the authors ability to statistically detect the potential beneficial effect of
471 PUFAs on cognitive function in a healthy aging population^{120 121 122} (Table 2). However, given the
472 positive effects found in cognitively impaired patients, the potential of a protective role of PUFAs
473 remains intriguing and should be further investigated with RCTs to fill this gap in the literature.

474

475 Given the importance of the MetS in the genesis of CVD, and the pivotal role of hypolipidemic
476 therapy in its prevention, it seemed reasonable to investigate the association of PUFA with the risk
477 of coronary heart disease and major cardiovascular events. A meta-analysis published in 2017¹²³
478 examined ten trials with a total of 77917 patients and found neither a positive nor a negative
479 association between omega-3 fatty acid supplementation and cardiovascular events.

480 Preclinical studies have highlighted a protective effect of PUFAs on brain tissue, due to the
481 antioxidant/anti-inflammatory action on the chronic low grade inflammation substrate generated by
482 MetS. However, studies on the preventative role of PUFAs on MCI and development of MetS are
483 currently lacking.

484

485 **The role of probiotics on MetS**

486 Probiotics are live microorganisms that have demonstrated beneficial effects on human health,
487 affecting multiples pathways and axes¹²⁴. Major sources of probiotics are yogurt and kefir. Due to
488 strong evidence that probiotics have anti-inflammatory properties, they could emerge as valuable
489 tool for ameliorating MetS outcomes.

490 Treatment with probiotics has been demonstrated to significantly reduce mean arterial pressure and
491 fasting plasma glucose, proving effectiveness in every MetS domain¹²⁵. Moreover, subjects treated
492 with probiotics showed a significant decrease in hs-CRP and TNF- α levels compared to the control
493 group, strengthening the hypothesis that probiotics may also improve MetS due to their anti-
494 inflammatory effects^{11 14 126}.

495 Some RCTs have been performed in elderly populations, more than ten of which, however, showed
496 confounders in the selection of the population (for example: type 2 diabetes subjects, or non-
497 standardized interventions, such as “Effects of kefir or milk supplementation”¹²⁷).

498 Cicero et al¹²⁸ found a reduction in prevalence of MetS, cardiovascular risk factors and markers of
499 insulin resistance in elderly patients through the 2-month period of treatment with a formula of *L.*
500 *plantarum* PBS067, *L. acidophilus* PBS066 and *L. reuteri* PBS072 with active prebiotics.
501 Specifically, the treatment group showed a statistically significant improvement in waist
502 circumference and in fasting plasma insulin, total cholesterol, high-density lipoprotein cholesterol,
503 non-HDL-C, TG, LDL-C. The exclusive effect on the plasma lipid profile was analyzed in a meta-
504 analysis of 13 RCTs conducted in patients with high, borderline and normal cholesterol¹²⁹. As a
505 result, the use of probiotics appeared to significantly lower total cholesterol and LDL, although with
506 no impact on HDL and TG. This effect was observed in all cohorts of subjects, and lipid profile at
507 the baseline did not influence the results (Table 2). This finding is important as it may open a path
508 for the possible use of probiotics in the prevention of hypercholesterolemia.

509

510 **The role of probiotics on MCI**

511 Emerging clinical and experimental evidence has highlighted a bidirectional relationship between
512 the gut microbiota and the brain, known as the microbiota-gut-brain axis (MGB)¹³⁰. Countless of
513 pathways are involved in this interconnection and a balanced composition of microbes is required
514 for its optimal functioning. In fact, activation of gut inflammation, due to dysbiosis, is believed to
515 be a cofactor in many pathological conditions; specifically, the microbiota has been proposed as a
516 key player in the pathogenesis of both neurodegeneration and MetS¹³¹. Therefore, restoring
517 homeostasis of gut microbiota could be a reasonable goal for medical therapy in MCI, for which a
518 medical therapy still needs to be codified.

519 To this end many efforts have been made to analyze the composition of microbiota in patients with
520 neurodegenerative disorders. The most characteristic alterations in gut microbiota flora observed in
521 patients with neurodegenerative disorders is the decrease in anti-inflammatory bacterial species
522 such as *Bifidobacterium breve strain A1* and increase in pro-inflammatory bacterial species such as
523 *Firmicutes* and *Bacteroidetes*^{124 132}. *Lactiplantibacillus Plantarum* has also been studied for its
524 anti-inflammatory properties, due to its high IL-10-inducing activity in immune cells^{133 134}.

525 Different studies with animal models^{135 136}, some RTCs^{137 138 139 140}, and an open label single arm
526 study¹⁴¹ have explored the possibility of restoring a correct proportion of microbiota as a potential
527 treatment for MCI, by administering probiotic *Bifidobacterium breve strain A1* supplements in mice
528 or patients diagnosed with MCI. These RCTs have tested similar amount of B. Breve CFU
529 comparing this treatment to placebo for different time lapse, such as B. breve MCC1274, 2×10¹⁰
530 CFU vs placebo for 24 weeks¹³⁷, B. breve A1, 2×10¹⁰ CFU vs placebo for 16 weeks¹³⁸, B. breve
531 MCC1274, 2×10¹⁰ CFU) or placebo for 16 weeks¹³⁹ and two capsules daily approximately
532 >2.0×10¹⁰ cfu B. breve A1 for 12 weeks vs placebo¹⁴⁰.

533 A meta-analysis run in 2020 by Den. et al¹²⁴ revealed a significant difference in cognitive
534 improvement between subjects with MCI or AD with and without probiotic supplementation.

535 Indeed, subjects treated with probiotics showed better cognitive function after supplementation. The
536 authors hypothesized that probiotics exert their effects by decreasing the level of inflammatory and
537 oxidative effectors, such as malondialdehyde (MDA) and high-sensitivity C-reactive protein (hs-
538 CRP), as these have been found to be significantly decreased in the probiotics versus control group
539 (Table 2).

540 However, no significant differences were observed at the level of total glutathione (GSH), nitric
541 oxide (NO) and total antioxidant capacity (TAC)¹²⁴. Although a relationship of causality needs to be
542 demonstrated, it is reasonable to note that immune signaling may not only be just a consequence of
543 neurodegeneration, but also a key player in its process. As a matter of fact, increasing evidence
544 demonstrates the relevance of inflammation in the progression of neurodegeneration^{142 143 144 145}. It
545 has been reported that individuals with higher levels of inflammatory proteins in the blood, decades
546 before the typical age of dementia symptom onset, are at increased risk for developing
547 neurodegenerative disease¹⁴⁵.

548 In studies on the effects of probiotics as a dietary supplement in subjects with MCI, results were
549 consistent with an improvement in the composite score of attention and working/verbal memory.
550 However, these studies present some limitations since the small population, the short observational
551 period and the limited selection of cognitive domains assessed limit the reliability of their results.
552 Therefore, increasing the sample size and improving the design of the trial could help clarify the
553 effect of probiotics on general brain function.

554

555 **The role of probiotics in the prevention of MCI/MetS**

556 Regarding the role of probiotics in the prevention of MCI, an interesting example of in utero use of
557 probiotics to ameliorate memory decline in later life was reported by Zhang et al¹⁴⁶. Using animal
558 models of lead-induced spatial memory deficit, maternal supplementation with *Lactobacillus*
559 *rhamnosus* at a dose of 10⁹ CFU/day has proven its potential to mitigate lead-induced memory

560 deficits. Notably, this result was independent of lead-induced alterations, as lead levels were
561 measured and were not significantly reduced after treatment. Furthermore, in vitro experiments
562 have revealed that *L. rhamnosus* inhibits growth of *E. coli*, a pathogen involved in memory
563 decline¹⁴⁷. Further research is needed to elucidate the mechanisms underlying probiotic-mediated
564 memory protection and its potential for broader application in cognitive impairment prevention¹⁴⁶.

565 Even with growing evidence from animal models supporting the use of therapies targeting gut
566 microbiota before birth, to protect against the development of MetS, their effects on pregnant
567 women are still unknown and these results require further research¹⁴⁸. However, animal models
568 offer a valid example of how environmental factors during pregnancy and lactation exert an
569 influence on adulthood development of MCI and MetS^{146 149}. With this awareness, various
570 prevention strategies in early life have been explored: as an example, as reviewed by Hsu et al,
571 supplementation with *Lactobacillus casei* during gestation in MetS induced rodent models, has been
572 shown to benefit hypertension in adult progenies¹⁵⁰.

573 The use of probiotics in the prevention of cognitive decline and metabolic features was also studied
574 by Davari et al¹⁵¹, who aimed to evaluate the effect of probiotics on plasma glucose and insulin
575 levels, behavioral tasks, and synaptic plasticity in a diabetic rat model. The Probiotics solution was
576 made by a mixture (each 334 mg) of *Lactobacillus acidophilus* (American type culture collection
577 (ATCC) 4356, 10^{10} CFU/g), *Bifidobacterium lactis* (Dutch chemical company (DSM) 10140,
578 10^{10} CFU/g) and *Lactobacillus fermentum* (ATCC 9338, 10^{10} CFU/g) and was administered for
579 8 weeks. It was effective in mitigating oxidative stress and inflammation and alleviating diabetic
580 complications. Indeed, results showed that supplementation with a probiotics solution (a mixture of
581 *Lactobacillus acidophilus*, *Bifidobacterium lactis* and *Lactobacillus fermentum*) significantly
582 improved spatial memory and task learning capabilities in diabetic animals. Moreover,
583 electrophysiological recordings revealed enhanced synaptic transmission compared to the control
584 group; biochemical measurements showed mitigated oxidative stress, as proven by increased level

585 of superoxide dismutase activity and reduced level of 8-hydroxydesoxyguanosin production.
586 Interestingly, no significant effects were observed on behaviour, synaptic plasticity, or biochemical
587 markers in control rats, suggesting that the potential therapeutic role of probiotics is specifically on
588 diabetes-related oxidative stress and neurodegeneration.

589 Mo et al¹⁵² explored the effects of probiotic supplementation in overweight human subjects,
590 showing how probiotics can positively influence some anthropometric parameters of MetS in
591 borderline-healthy patients. *Lactobacillus curvatus* HY7601 and *Lactobacillus plantarum* KY1032
592 were administered orally for 12 weeks, resulting in a reduction in visceral fat mass and waist
593 circumference, along with an increase in adiponectin levels. This positive impact could be triggered
594 by a modulation of gut microbiota, presented here as a key determinant for activation of specific
595 signaling pathways in obese humans. This RCT¹⁵² suggests how probiotics could be used as a
596 promising strategy for the prevention of obesity and related metabolic disorders (Table 2).

597 In conclusion, we can say that studies on the effect of probiotics MetS and MCI show contrasting
598 results. However, given the lack of RCTs with standardized outcome in the literature, more research
599 is needed in order to clarify whether these nutraceuticals can be validated as codified treatment for
600 both MetS and MCI.

601

602 **Conclusions**

603 The study of nutraceuticals is an emerging field of growing interest due to the necessity for
604 strategies in the prevention and treatment of MetS and MCI. These conditions are strongly
605 connected, and both are a prelude to more severe outcomes. Since MetS and MCI share
606 pathophysiological pathways, the keys of which are inflammation and oxidative stress, substances
607 with antioxidant and anti-inflammatory properties have been explored in healthy and impaired
608 models, with heterogeneous results. While there is sufficient literature on the biochemical effects of

609 some nutraceuticals, there is still limited evidence for the positive effects of vitamin E, PUFAs,
610 probiotics and resveratrol on subjects with impaired cognitive function or metabolic syndrome and
611 weak evidence supporting the intervention with these nutraceuticals as prevention. The literature
612 lacks studies with standardized interventions, clear and codified cognitive and metabolic
613 assessments, and specific pathognomonic biomarkers of MetS and MCI. Also, considering the long-
614 term requirement of medications when it comes to MetS and MCI, longer trials and observational
615 studies in this area are needed. In particular, we stress the need for RCTs with more rigorous end
616 points and more specific markers which can provide reliable evidence to assess the adequacy of
617 interventions with nutraceuticals.

618

619 **Limitations of study**

620 Firstly, the narrative character of this study represent itself a limitation. As a matter of fact, the
621 unsystematic selection, lacked formal metanalytic method to derive the most trustable RCTs from
622 the existing literature, could have produced a biased study selection. Secondary, we have not
623 organized our review by mechanisms of actions or biological origin of components, which
624 represents another flaw. Finally, the preclinical character of MCI and MetS represents an obstacle
625 for rigorous identification of population and outcome, leading us to include a variety of studies that
626 are often too different from each other to be reproducible.

627

628 **Declaration of interests**

629 The authors declare no competing interests.

630 **Bibliography**

- 631 1. Fahed, G., Aoun, L., Zerdan, M.B., Allam, S., Zerdan, M.B., Bouferraa, Y., and Assi, H.I.
632 (2022). Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. *Int. J.*
633 *Mol. Sci.* 23. <https://doi.org/10.3390/ijms23020786>.

- 634 2. Mezza, T., Cefalo, C.M.A., Cinti, F., Quero, G., Pontecorvi, A., Alfieri, S., Holst, J.J., and
635 Giaccari, A. (2020). Endocrine and Metabolic Insights from Pancreatic Surgery. *Trends*
636 *Endocrinol. Metab.* *31*, 760–772. <https://doi.org/10.1016/j.tem.2020.07.003>.
- 637 3. Tahmi, M., Palta, P., and Luchsinger, J.A. (2021). Metabolic Syndrome and Cognitive
638 Function. *Curr. Cardiol. Rep.* *23*, 180. <https://doi.org/10.1007/s11886-021-01615-y>.
- 639 4. Wang, X., Ji, L., Tang, Z., Ding, G., Chen, X., Lv, J., Chen, Y., and Li, D. (2021). The
640 association of metabolic syndrome and cognitive impairment in Jidong of China: a cross-
641 sectional study. *BMC Endocr. Disord.* *21*, 1–8. <https://doi.org/10.1186/s12902-021-00705-w>.
- 642 5. Hao, Z., Wu, B., Wang, D., and Liu, M. (2011). Association between metabolic syndrome
643 and cognitive decline: A systematic review of prospective population-based studies. *Acta*
644 *Neuropsychiatr.* *23*, 69–74. <https://doi.org/10.1111/j.1601-5215.2011.00527.x>.
- 645 6. Panza, F., Frisardi, V., Capurso, C., Imbimbo, B.P., Vendemiale, G., Santamato, A.,
646 D’Onofrio, G., Seripa, D., Sancarlo, D., Pilotto, A., et al. (2010). Metabolic syndrome and
647 cognitive impairment: Current epidemiology and possible underlying mechanisms. *J.*
648 *Alzheimer’s Dis.* *21*, 691–724. <https://doi.org/10.3233/JAD-2010-091669>.
- 649 7. Tsai, C.K., Kao, T.W., Lee, J.T., Wu, C.J., Hueng, D.Y., Liang, C.S., Wang, G.C., Yang,
650 F.C., and Chen, W.L. (2016). Increased risk of cognitive impairment in patients with
651 components of metabolic syndrome. *Med. (United States)* *95*.
652 <https://doi.org/10.1097/MD.00000000000004791>.
- 653 8. Frisardi, V., Solfrizzi, V., Seripa, D., Capurso, C., Santamato, A., Sancarlo, D., Vendemiale,
654 G., Pilotto, A., and Panza, F. (2010). Metabolic-cognitive syndrome: A cross-talk between
655 metabolic syndrome and Alzheimer’s disease. *Ageing Res. Rev.* *9*, 399–417.
656 <https://doi.org/10.1016/j.arr.2010.04.007>.
- 657 9. Ambroselli, D., Masciulli, F., Romano, E., Catanzaro, G., Besharat, Z.M., Massari, M.C.,
658 Ferretti, E., Migliaccio, S., Izzo, L., Ritieni, A., et al. (2023). New Advances in Metabolic
659 Syndrome, from Prevention to Treatment: The Role of Diet and Food. *Nutrients* *15*.
660 <https://doi.org/10.3390/nu15030640>.
- 661 10. Calder, P.C. (2022). Dietary factors and low-grade inflammation in relation to overweight
662 and obesity revisited. *Br. J. Nutr.* *127*, 1455–1457.
663 <https://doi.org/10.1017/S0007114522000782>.
- 664 11. Debnath, M., Agrawal, S., Agrawal, A., and Dubey, G.P. (2016). Metaflammatory responses
665 during obesity: Pathomechanism and treatment. *Obes. Res. Clin. Pract.* *10*, 103–113.
666 <https://doi.org/10.1016/j.orcp.2015.10.012>.
- 667 12. Barchetta, I., Cimini, F.A., Ciccarelli, G., Baroni, M.G., and Cavallo, M.G. (2019). Sick fat:
668 the good and the bad of old and new circulating markers of adipose tissue inflammation. *J.*
669 *Endocrinol. Invest.* *42*, 1257–1272. <https://doi.org/10.1007/s40618-019-01052-3>.
- 670 13. Frisardi, V., Solfrizzi, V., Capurso, C., Imbimbo, B.P., Vendemiale, G., Seripa, D., Pilotto,
671 A., and Panza, F. (2010). Is insulin resistant brain state a central feature of the metabolic-
672 cognitive syndrome? *J. Alzheimer’s Dis.* *21*, 57–63. <https://doi.org/10.3233/JAD-2010-100015>.
- 674 14. Kelly, K.R., Haus, J.M., Solomon, T.P.J., Patrick-Melin, A.J., Cook, M., Rocco, M.,
675 Barkoukis, H., and Kirwan, J.P. (2011). A low-glycemic index diet and exercise intervention
676 reduces TNF α in isolated mononuclear cells of older, obese adults. *J. Nutr.* *141*, 1089–1094.
677 <https://doi.org/10.3945/jn.111.139964>.

- 678 15. Guillemot-Legris, O., and Muccioli, G.G. (2017). Obesity-Induced Neuroinflammation:
679 Beyond the Hypothalamus. *Trends Neurosci.* *40*, 237–253.
680 <https://doi.org/10.1016/j.tins.2017.02.005>.
- 681 16. Miranda, P.J., DeFronzo, R.A., Califf, R.M., and Guyton, J.R. (2005). Metabolic syndrome:
682 Definition, pathophysiology, and mechanisms. *Am. Heart J.* *149*, 33–45.
683 <https://doi.org/10.1016/j.ahj.2004.07.013>.
- 684 17. Al Haj Ahmad, R.M., Ababneh, N.A., and Al-Domi, H.A. (2022). Brain insulin resistance as
685 a mechanistic mediator links peripheral metabolic disorders with declining cognition.
686 *Diabetes Metab. Syndr. Clin. Res. Rev.* *16*, 102468.
687 <https://doi.org/10.1016/j.dsx.2022.102468>.
- 688 18. Frazier, H.N., Ghoweri, A.O., Anderson, K.L., Lin, R.L., Porter, N.M., and Thibault, O.
689 (2019). Broadening the definition of brain insulin resistance in aging and Alzheimer’s
690 disease. *Exp. Neurol.* *313*, 79–87. <https://doi.org/10.1016/j.expneurol.2018.12.007>.
- 691 19. Kim, B., and Feldman, E.L. (2015). Insulin resistance as a key link for the increased risk of
692 cognitive impairment in the metabolic syndrome. *Exp. Mol. Med.* *47*.
693 <https://doi.org/10.1038/EMM.2015.3>.
- 694 20. Hölscher, C. (2014). The incretin hormones glucagonlike peptide 1 and glucose-dependent
695 insulinotropic polypeptide are neuroprotective in mouse models of Alzheimer’s disease.
696 *Alzheimer’s Dement.* *10*. <https://doi.org/10.1016/j.jalz.2013.12.009>.
- 697 21. Rizzo, M.R., Di Meo, I., Polito, R., Auriemma, M.C., Gambardella, A., di Mauro, G.,
698 Capuano, A., and Paolisso, G. (2022). Cognitive impairment and type 2 diabetes mellitus:
699 Focus of SGLT2 inhibitors treatment. *Pharmacol. Res.* *176*, 106062.
700 <https://doi.org/10.1016/j.phrs.2022.106062>.
- 701 22. Srikanth, V., Sinclair, A.J., Hill-Briggs, F., Moran, C., and Biessels, G.J. (2020). Type 2
702 diabetes and cognitive dysfunction—towards effective management of both comorbidities.
703 *Lancet Diabetes Endocrinol.* *8*, 535–545. [https://doi.org/10.1016/S2213-8587\(20\)30118-2](https://doi.org/10.1016/S2213-8587(20)30118-2).
- 704 23. Anderson, N.D. (2019). State of the science on mild cognitive impairment (MCI). *CNS*
705 *Spectr.* *24*, 78–87. <https://doi.org/10.1017/S1092852918001347>.
- 706 24. Di Majo, D., Ricciardi, N., Di Liberto, V., Allegra, M., Frinchi, M., Urone, G., Scordino, M.,
707 Massaro, A., Mudò, G., Ferraro, G., et al. (2024). The remarkable impact of *Opuntia Ficus*
708 *Indica* fruit administration on metabolic syndrome: Correlations between cognitive functions,
709 oxidative stress and lipid dysmetabolism in the high-fat, diet-fed rat model. *Biomed.*
710 *Pharmacother.* *177*. <https://doi.org/10.1016/j.biopha.2024.117028>.
- 711 25. Johnson, L.A., Zuloaga, K.L., Kugelman, T.L., Mader, K.S., Morré, J.T., Zuloaga, D.G.,
712 Weber, S., Marzulla, T., Mulford, A., Button, D., et al. (2016). Amelioration of Metabolic
713 Syndrome-Associated Cognitive Impairments in Mice via a Reduction in Dietary Fat Content
714 or Infusion of Non-Diabetic Plasma. *EBioMedicine* *3*, 26–42.
715 <https://doi.org/10.1016/j.ebiom.2015.12.008>.
- 716 26. Komulainen, P., Tuomilehto, J., Savonen, K., Männikkö, R., Hassinen, M., Lakka, T.A.,
717 Hänninen, T., Kiviniemi, V., Jacobs, D.R., Kivipelto, M., et al. (2021). Exercise, diet, and
718 cognition in a 4-year randomized controlled trial: Dose-Responses to Exercise Training
719 (DR’s EXTRA). *Am. J. Clin. Nutr.* *113*, 1428–1439. <https://doi.org/10.1093/ajcn/nqab018>.
- 720 27. Frisardi, V., Panza, F., Seripa, D., Imbimbo, B.P., Vendemiale, G., Pilotto, A., and Solfrizzi,
721 V. (2010). Nutraceutical properties of mediterranean diet and cognitive decline: Possible

- 722 underlying mechanisms. *J. Alzheimer's Dis.* 22, 715–740. [https://doi.org/10.3233/JAD-2010-](https://doi.org/10.3233/JAD-2010-100942)
723 100942.
- 724 28. Di Murro, E., Di Giuseppe, G., Soldovieri, L., Moffa, S., Improta, I., Capece, U., Nista, E.C.,
725 Cinti, F., Ciccarelli, G., Brunetti, M., et al. (2023). Physical Activity and Type 2 Diabetes: In
726 Search of a Personalized Approach to Improving β -Cell Function. *Nutrients* 15, 1–16.
727 <https://doi.org/10.3390/nu15194202>.
- 728 29. DI Giuseppe, G., Ciccarelli, G., Cefalo, C.M., Cinti, F., Moffa, S., Impronta, F., Capece, U.,
729 Pontecorvi, A., Giaccari, A., and Mezza, T. (2021). Prediabetes: how pathophysiology drives
730 potential intervention on a subclinical disease with feared clinical consequences. *Minerva*
731 *Endocrinol.* 46, 272–292. <https://doi.org/10.23736/S2724-6507.21.03405-9>.
- 732 30. Puri, S., Shaheen, M., and Grover, B. (2023). Nutrition and cognitive health: A life course
733 approach. *Front. Public Heal.* 11, 1–11. <https://doi.org/10.3389/fpubh.2023.1023907>.
- 734 31. Dominguez, L.J., Veronese, N., Vernuccio, L., Catanese, G., Inzerillo, F., Salemi, G., and
735 Barbagallo, M. (2021). Nutrition, physical activity, and other lifestyle factors in the
736 prevention of cognitive decline and dementia. *Nutrients* 13, 1–60.
737 <https://doi.org/10.3390/nu13114080>.
- 738 32. Moffa, S., Improta, I., Rocchetti, S., Mezza, T., and Giaccari, A. (2019). Potential cause-
739 effect relationship between insulin autoimmune syndrome and alpha lipoic acid: Two case
740 reports. *Nutrition* 57, 1–4. <https://doi.org/10.1016/j.nut.2018.04.010>.
- 741 33. Capece, U., Moffa, S., Improta, I., Di Giuseppe, G., Nista, E.C., Cefalo, C.M.A., Cinti, F.,
742 Pontecorvi, A., Gasbarrini, A., Giaccari, A., et al. (2023). Alpha-Lipoic Acid and Glucose
743 Metabolism: A Comprehensive Update on Biochemical and Therapeutic Features. *Nutrients*
744 15, 1–19. <https://doi.org/10.3390/nu15010018>.
- 745 34. Daliu, P., Santini, A., and Novellino, E. (2019). From pharmaceuticals to nutraceuticals:
746 bridging disease prevention and management. *Expert Rev. Clin. Pharmacol.* 12, 1–7.
747 <https://doi.org/10.1080/17512433.2019.1552135>.
- 748 35. Lloret, A., Badía, M.C., Mora, N.J., Pallardó, F. V., Alonso, M.D., and Viña, J. (2009).
749 Vitamin e paradox in alzheimer's disease: It does not prevent loss of cognition and may even
750 be detrimental. *J. Alzheimer's Dis.* 17, 143–149. <https://doi.org/10.3233/JAD-2009-1033>.
- 751 36. Nusret Engin, K. (2009). Alpha-tocopherol: looking beyond an antioxidant. *Mol. Vis.* 15,
752 855–860.
- 753 37. Wong, S.K., Chin, K.Y., Suhaimi, F.H., Ahmad, F., and Ima-Nirwana, S. (2017). Vitamin E
754 as a potential interventional treatment for metabolic syndrome: Evidence from animal and
755 human studies. *Front. Pharmacol.* 8, 1–12. <https://doi.org/10.3389/fphar.2017.00444>.
- 756 38. Zhao, L., Kang, I., Fang, X., Wang, W., Lee, M.A., Hollins, R.R., Marshall, M.R., and
757 Chung, S. (2015). Gamma-tocotrienol attenuates high-fat diet-induced obesity and insulin
758 resistance by inhibiting adipose inflammation and M1 macrophage recruitment. *Int. J. Obes.*
759 (Lond). 39, 438–446. <https://doi.org/10.1038/ijo.2014.124>.
- 760 39. Mice, D. (2022). Tocotrienols Attenuate White Adipose Tissue Accumulation.
- 761 40. Manzella, D., Barbieri, M., Ragno, E., and Paolisso, G. (2001). Chronic administration of
762 pharmacologic doses of vitamin E improves the cardiac autonomic nervous system in
763 patients with type 2 diabetes. *Am. J. Clin. Nutr.* 73, 1052–1057.
764 <https://doi.org/10.1093/ajcn/73.6.1052>.

- 765 41. Paolisso, G., Di Maro, G., Galzerano, D., Cacciapuoti, F., Varricchio, G., Varricchio, M., and
 766 D'Onofrio, F. (1994). Pharmacological doses of vitamin E and insulin action in elderly
 767 subjects. *Am. J. Clin. Nutr.* *59*, 1291–1296. <https://doi.org/10.1093/ajcn/59.6.1291>.
- 768 42. Pazdro, R., and Burgess, J.R. (2010). The role of vitamin E and oxidative stress in diabetes
 769 complications. *Mech. Ageing Dev.* *131*, 276–286. <https://doi.org/10.1016/j.mad.2010.03.005>.
- 770 43. Mezza, T., Shirakawa, J., Martinez, R., Hu, J., Giaccari, A., and Kulkarni, R.N. (2016).
 771 Nuclear export of FoxO1 is associated with ERK signaling in β -cells lacking insulin
 772 receptors. *J. Biol. Chem.* *291*, 21485–21495. <https://doi.org/10.1074/jbc.M116.735738>.
- 773 44. Mezza, T., Ferraro, P.M., Giuseppe, G. Di, Moffa, S., Cefalo, C.M.A., Cinti, F., Impronta, F.,
 774 Capece, U., Quero, G., Pontecorvi, A., et al. (2021). Pancreaticoduodenectomy model
 775 demonstrates a fundamental role of dysfunctional β cells in predicting diabetes. *J. Clin.*
 776 *Invest.* *131*. <https://doi.org/10.1172/JCI146788>.
- 777 45. Asayama, K., Kooy, N.W., and Burr, I.M. (1986). Effect of vitamin E deficiency and
 778 selenium deficiency on insulin secretory reserve and free radical scavenging systems in
 779 islets: decrease of islet manganosuperoxide dismutase. *J. Lab. Clin. Med.* *107*, 459–464.
- 780 46. Mahdy, Z.A., Siraj, H.H., Khaza'ai, H., Mutalib, M.S.A., Azwar, M.H., Wahab, M.A., Dali,
 781 A.Z.H.M., Jaafar, R., Ismail, N.A.M., Jamil, M.A., et al. (2013). Does palm oil vitamin E
 782 reduce the risk of pregnancy induced hypertension? *Acta medica (Hradec Kral.* *56*, 104–109.
 783 <https://doi.org/10.14712/18059694.2014.17>.
- 784 47. Aminuddin, N.A., Sutan, R., and Mahdy, Z.A. (2021). Role of Palm Oil Vitamin E in
 785 Preventing Pre-eclampsia: A Secondary Analysis of a Randomized Clinical Trial Following
 786 ISSHP Reclassification. *Front. Med.* *7*, 1–8. <https://doi.org/10.3389/fmed.2020.596405>.
- 787 48. Taddei, S., Virdis, A., Ghiadoni, L., Magagna, A., and Salvetti, A. (1998). Vitamin C
 788 improves endothelium-dependent vasodilation by restoring nitric oxide activity in essential
 789 hypertension. *Circulation* *97*, 2222–2229. <https://doi.org/10.1161/01.CIR.97.22.2222>.
- 790 49. Ceriello, A., Giugliano, D., Quatraro, A., and Lefebvre, P.J. (1991). Anti-oxidants show an
 791 anti-hypertensive effect in diabetic and hypertensive subjects. *Clin. Sci.* *81*, 739–742.
 792 <https://doi.org/10.1042/cs0810739>.
- 793 50. Palumbo, G., Avanzini, F., Alli, C., Roncaglioni, M.C., Ronchi, E., Cristofari, M., Capra, A.,
 794 Rossi, S., Nosotti, L., Costantini, C., et al. (2000). Effects of vitamin E on clinic and
 795 ambulatory blood pressure in treated hypertensive patients. *Am. J. Hypertens.* *13*, 564–567.
 796 [https://doi.org/10.1016/s0895-7061\(00\)00244-2](https://doi.org/10.1016/s0895-7061(00)00244-2).
- 797 51. Economides, P.A., Khaodhiar, L., Caselli, A., Caballero, A.E., Keenan, H., Bursell, S.E.,
 798 King, G.L., Johnstone, M.T., Horton, E.S., and Veves, A. (2005). The effect of vitamin E on
 799 endothelial function of micro- and macrocirculation and left ventricular function in type 1
 800 and type 2 diabetic patients. *Diabetes* *54*, 204–211. <https://doi.org/10.2337/diabetes.54.1.204>.
- 801 52. Farina, N., Llewellyn, D., Isaac, M.G.E.K.N., and Tabet, N. (2017). Vitamin E for
 802 Alzheimer's dementia and mild cognitive impairment. *Cochrane Database Syst. Rev.* *2017*.
 803 <https://doi.org/10.1002/14651858.CD002854.pub4>.
- 804 53. Lakhan, R., Sharma, M., Batra, K., and Beatty, F.B. (2021). The role of vitamin e in slowing
 805 down mild cognitive impairment: A narrative review. *Healthc.* *9*, 1–12.
 806 <https://doi.org/10.3390/healthcare9111573>.
- 807 54. Gugliandolo, A., Bramanti, P., and Mazzon, E. (2017). Role of vitamin e in the treatment of

- 808 alzheimer's disease: Evidence from animal models. *Int. J. Mol. Sci.* *18*.
809 <https://doi.org/10.3390/ijms18122504>.
- 810 55. Kaneai, N., Arai, M., Takatsu, H., Fukui, K., and Urano, S. (2012). Vitamin e inhibits
811 oxidative stress-induced denaturation of nerve terminal proteins involved in
812 neurotransmission. *J. Alzheimer's Dis.* *28*, 183–189. [https://doi.org/10.3233/JAD-2011-](https://doi.org/10.3233/JAD-2011-111133)
813 [111133](https://doi.org/10.3233/JAD-2011-111133).
- 814 56. Ulatowski, L.M., and Manor, D. (2015). Vitamin E and neurodegeneration. *Neurobiol. Dis.*
815 *84*, 78–83. <https://doi.org/10.1016/j.nbd.2015.04.002>.
- 816 57. Rota, C., Rimbach, G., Minihane, A.M., Stoecklin, E., and Barella, L. (2005). Dietary
817 vitamin E modulates differential gene expression in the rat hippocampus: Potential
818 implications for its neuroprotective properties. *Nutr. Neurosci.* *8*, 21–29.
819 <https://doi.org/10.1080/10284150400027123>.
- 820 58. Isaac, M.G.E.K.N., Quinn, R., and Tabet, N. (2008). Vitamin E for Alzheimer's disease and
821 mild cognitive impairment. *Cochrane database Syst. Rev.*, CD002854.
822 <https://doi.org/10.1002/14651858.CD002854.pub2>.
- 823 59. Giraldo, E., Lloret, A., Fuchsberger, T., and Viña, J. (2014). A β and tau toxicities in
824 Alzheimer's are linked via oxidative stress-induced p38 activation: Protective role of vitamin
825 E. *Redox Biol.* *2*, 873–877. <https://doi.org/10.1016/j.redox.2014.03.002>.
- 826 60. Dominguez, L.J., and Barbagallo, M. (2018). Nutritional prevention of cognitive decline and
827 dementia. *Acta Biomed.* *89*, 276–290. <https://doi.org/10.23750/abm.v89i2.7401>.
- 828 61. Maxwell, C.J., Hicks, M.S., Hogan, D.B., Basran, J., and Ebly, E.M. (2005). Supplemental
829 use of antioxidant vitamins and subsequent risk of cognitive decline and dementia. *Dement.*
830 *Geriatr. Cogn. Disord.* *20*, 45–51. <https://doi.org/10.1159/000085074>.
- 831 62. Morris, M.C., Schneider, J.A., Li, H., Tangney, C.C., Nag, S., Bennett, D.A., Honer, W.G.,
832 and Barnes, L.L. (2015). Brain tocopherols related to Alzheimer's disease neuropathology in
833 humans. *Alzheimer's Dement.* *11*, 32–39. <https://doi.org/10.1016/j.jalz.2013.12.015>.
- 834 63. Jae, H.K., Cook, N., Manson, J.A., Buring, J.E., and Grodstein, F. (2006). A randomized trial
835 of vitamin E supplementation and cognitive function in women. *Arch. Intern. Med.* *166*,
836 *2462–2468*. <https://doi.org/10.1001/archinte.166.22.2462>.
- 837 64. Nagib, M.M., Tadros, M.G., Rahmo, R.M., Sabri, N.A., Khalifa, A.E., and Masoud, S.I.
838 (2019). Ameliorative Effects of α -Tocopherol and/or Coenzyme Q10 on Phenytoin-Induced
839 Cognitive Impairment in Rats: Role of VEGF and BDNF-TrkB-CREB Pathway. *Neurotox.*
840 *Res.* *35*, 451–462. <https://doi.org/10.1007/s12640-018-9971-6>.
- 841 65. Ramis, M.R., Sarubbo, F., Terrasa, J.L., Moranta, D., Aparicio, S., Miralles, A., and Esteban,
842 S. (2015). Chronic α -Tocopherol Increases Central Monoamines Synthesis and Improves
843 Cognitive and Motor Abilities in Old Rats. *Rejuvenation Res.* *19*, 159–171.
844 <https://doi.org/10.1089/rej.2015.1685>.
- 845 66. Qureshi, A.A., Sami, S.A., Salser, W.A., and Khan, F.A. (2001). Synergistic effect of
846 tocotrienol-rich fraction (TRF(25)) of rice bran and lovastatin on lipid parameters in
847 hypercholesterolemic humans. *J. Nutr. Biochem.* *12*, 318–329. [https://doi.org/10.1016/s0955-](https://doi.org/10.1016/s0955-2863(01)00144-9)
848 [2863\(01\)00144-9](https://doi.org/10.1016/s0955-2863(01)00144-9).
- 849 67. Qi, X., Guo, J., Li, Y., Fang, C., Lin, J., Chen, X., and Jia, J. (2024). Vitamin E intake is
850 inversely associated with NAFLD measured by liver ultrasound transient elastography. *Sci.*

- 851 Rep. *14*, 1–11. <https://doi.org/10.1038/s41598-024-52482-w>.
- 852 68. Ciccarelli, G., Di Giuseppe, G., Cinti, F., Moffa, S., Mezza, T., and Giaccari, A. (2023). Why
853 do some glucose-lowering agents improve non-alcoholic fatty liver disease whereas others do
854 not? A narrative review in search of a unifying hypothesis. *Diabetes. Metab. Res. Rev.* *39*.
855 <https://doi.org/10.1002/dmrr.3668>.
- 856 69. Kato, Y., Aoki, Y., and Fukui, K. (2020). Tocotrienols influence body weight gain and brain
857 protein expression in long-term high-fat diet-treated mice. *Int. J. Mol. Sci.* *21*, 1–14.
858 <https://doi.org/10.3390/ijms21124533>.
- 859 70. Kato, Y., Ben, J., Noto, A., Kashiwaya, S., Aoki, Y., Watanabe, N., Tsumoto, H., Miura, Y.,
860 and Fukui, K. (2024). Tocotrienols Prevent the Decline of Learning Ability in High-Fat,
861 High-Sucrose Diet-Fed C57BL/6 Mice. *Int. J. Mol. Sci.* *25*.
862 <https://doi.org/10.3390/ijms25063561>.
- 863 71. Signorelli, P., and Ghidoni, R. (2005). Resveratrol as an anticancer nutrient: Molecular basis,
864 open questions and promises. *J. Nutr. Biochem.* *16*, 449–466.
865 <https://doi.org/10.1016/j.jnutbio.2005.01.017>.
- 866 72. Dixon, R.A. (2001). Natural products and plant disease resistance. *Nature* *411*, 843–847.
867 <https://doi.org/10.1038/35081178>.
- 868 73. López-Rodríguez, R., Domínguez, L., Fernández-Ruiz, V., and Cámara, M. (2022). Extracts
869 Rich in Nutrients as Novel Food Ingredients to Be Used in Food Supplements: A Proposal
870 Classification. *Nutrients* *14*. <https://doi.org/10.3390/nu14153194>.
- 871 74. Szkudelski, T., and Szkudelska, K. (2015). Resveratrol and diabetes: From animal to human
872 studies. *Biochim. Biophys. Acta - Mol. Basis Dis.* *1852*, 1145–1154.
873 <https://doi.org/10.1016/j.bbadis.2014.10.013>.
- 874 75. Baile, C.A., Yang, J.Y., Rayalam, S., Hartzell, D.L., Lai, C.Y., Andersen, C., and Della-Fera,
875 M.A. (2011). Effect of resveratrol on fat mobilization. *Ann. N. Y. Acad. Sci.* *1215*, 40–47.
876 <https://doi.org/10.1111/j.1749-6632.2010.05845.x>.
- 877 76. Cimini, F.A., Barchetta, I., Ciccarelli, G., Leonetti, F., Silecchia, G., Chiappetta, C., Di
878 Cristofano, C., Capoccia, D., Bertocchini, L., Ceccarelli, V., et al. (2021). Adipose tissue
879 remodelling in obese subjects is a determinant of presence and severity of fatty liver disease.
880 *Diabetes. Metab. Res. Rev.* *37*, 1–9. <https://doi.org/10.1002/dmrr.3358>.
- 881 77. Kim, E.N., Kim, M.Y., Lim, J.H., Kim, Y., Shin, S.J., Park, C.W., Kim, Y.S., Chang, Y.S.,
882 Yoon, H.E., and Choi, B.S. (2018). The protective effect of resveratrol on vascular aging by
883 modulation of the renin–angiotensin system. *Atherosclerosis* *270*, 123–131.
884 <https://doi.org/10.1016/j.atherosclerosis.2018.01.043>.
- 885 78. Dolinsky, V.W., Chakrabarti, S., Pereira, T.J., Oka, T., Levasseur, J., Beker, D., Zordoky,
886 B.N., Morton, J.S., Nagendran, J., Lopaschuk, G.D., et al. (2013). Resveratrol prevents
887 hypertension and cardiac hypertrophy in hypertensive rats and mice. *Biochim. Biophys. Acta*
888 *- Mol. Basis Dis.* *1832*, 1723–1733. <https://doi.org/10.1016/j.bbadis.2013.05.018>.
- 889 79. Asgary, S., Karimi, R., Momtaz, S., Naseri, R., and Farzaei, M.H. (2019). Effect of
890 resveratrol on metabolic syndrome components: A systematic review and meta-analysis. *Rev.*
891 *Endocr. Metab. Disord.* *20*, 173–186. <https://doi.org/10.1007/s11154-019-09494-z>.
- 892 80. Buglio, D.S., Marton, L.T., Laurindo, L.F., Guiguer, E.L., Araújo, A.C., Buchaim, R.L.,
893 Goulart, R. de A., Rubira, C.J., and Barbalho, S.M. (2022). The Role of Resveratrol in Mild

- 894 Cognitive Impairment and Alzheimer's Disease: A Systematic Review. *J. Med. Food* 25,
895 797–806. <https://doi.org/10.1089/jmf.2021.0084>.
- 896 81. Zhou, D.D., Luo, M., Huang, S.Y., Saimaiti, A., Shang, A., Gan, R.Y., and Li, H. Bin
897 (2021). Effects and Mechanisms of Resveratrol on Aging and Age-Related Diseases. *Oxid.*
898 *Med. Cell. Longev.* 2021. <https://doi.org/10.1155/2021/9932218>.
- 899 82. Köbe, T., Witte, A.V., Schnelle, A., Tesky, V.A., Pantel, J., Schuchardt, J.P., Hahn, A.,
900 Bohlken, J., Grittner, U., and Flöel, A. (2017). Impact of resveratrol on glucose control,
901 hippocampal structure and connectivity, and memory performance in patients with mild
902 cognitive impairment. *Front. Neurosci.* 11, 1–11. <https://doi.org/10.3389/fnins.2017.00105>.
- 903 83. Gocmez, S.S., Gacar, N., Utkan, T., Gacar, G., Scarpace, P.J., and Tumer, N. (2016).
904 Protective effects of resveratrol on aging-induced cognitive impairment in rats. *Neurobiol.*
905 *Learn. Mem.* 131, 131–136. <https://doi.org/10.1016/j.nlm.2016.03.022>.
- 906 84. Li, H.F., Chen, S.A., and Wu, S.N. (2000). Evidence for the stimulatory effect of resveratrol
907 on Ca²⁺-activated K⁺ current in vascular endothelial cells. *Cardiovasc. Res.* 45, 1035–1045.
908 [https://doi.org/10.1016/S0008-6363\(99\)00397-1](https://doi.org/10.1016/S0008-6363(99)00397-1).
- 909 85. Veronica Witte, A., Kerti, L., Margulies, D.S., and Flöel, A. (2014). Effects of resveratrol on
910 memory performance, hippocampal functional connectivity, and glucose metabolism in
911 healthy older adults. *J. Neurosci.* 34, 7862–7870. [https://doi.org/10.1523/JNEUROSCI.0385-](https://doi.org/10.1523/JNEUROSCI.0385-14.2014)
912 14.2014.
- 913 86. Porquet, D., Griñán-Ferré, C., Ferrer, I., Camins, A., Sanfeliu, C., Del Valle, J., and Pallàs,
914 M. (2014). Neuroprotective role of trans-resveratrol in a murine model of familial
915 alzheimer's disease. *J. Alzheimer's Dis.* 42, 1209–1220. [https://doi.org/10.3233/JAD-](https://doi.org/10.3233/JAD-140444)
916 140444.
- 917 87. Dolinsky, V.W., Rueda-Clausen, C.F., Morton, J.S., Davidge, S.T., and Dyck, J.R.B. (2011).
918 Continued postnatal administration of resveratrol prevents diet-induced metabolic syndrome
919 in rat offspring born growth restricted. *Diabetes* 60, 2274–2284.
920 <https://doi.org/10.2337/db11-0374>.
- 921 88. Izquierdo, V., Palomera-Ávalos, V., López-Ruiz, S., Canudas, A.M., Pallàs, M., and Griñán-
922 Ferré, C. (2019). Maternal resveratrol supplementation prevents cognitive decline in
923 senescent mice offspring. *Int. J. Mol. Sci.* 20. <https://doi.org/10.3390/ijms20051134>.
- 924 89. Wu, Z., Chen, T., Pan, D., Zeng, X., Guo, Y., and Zhao, G. (2021). Resveratrol and organic
925 selenium-rich fermented milk reduces D-galactose-induced cognitive dysfunction in mice.
926 *Food Funct.* 12, 1318–1326. <https://doi.org/10.1039/d0fo02029j>.
- 927 90. Timmers, S., Konings, E., Bilet, L., Houtkooper, R.H., Van De Weijer, T., Goossens, G.H.,
928 Hoeks, J., Van Der Krieken, S., Ryu, D., Kersten, S., et al. (2011). Calorie restriction-like
929 effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile
930 in obese humans. *Cell Metab.* 14, 612–622. <https://doi.org/10.1016/j.cmet.2011.10.002>.
- 931 91. Konings, E., Timmers, S., Boekschoten, M. V., Goossens, G.H., Jocken, J.W., Afman, L.A.,
932 Müller, M., Schrauwen, P., Mariman, E.C., and Blaak, E.E. (2014). The effects of 30 days
933 resveratrol supplementation on adipose tissue morphology and gene expression patterns in
934 obese men. *Int. J. Obes.* 38, 470–473. <https://doi.org/10.1038/ijo.2013.155>.
- 935 92. Gocmez, S.S., Şahin, T.D., Yazir, Y., Duruksu, G., Eraldemir, F.C., Polat, S., and Utkan, T.
936 (2019). Resveratrol prevents cognitive deficits by attenuating oxidative damage and
937 inflammation in rat model of streptozotocin diabetes induced vascular dementia. *Physiol.*

- 938 Behav. 201, 198–207. <https://doi.org/10.1016/j.physbeh.2018.12.012>.
- 939 93. Tian, X., Liu, Y., Ren, G., Yin, L., Liang, X., Geng, T., Dang, H., and An, R. (2016).
940 Resveratrol limits diabetes-associated cognitive decline in rats by preventing oxidative stress
941 and inflammation and modulating hippocampal structural synaptic plasticity. *Brain Res.*
942 *1650*, 1–9. <https://doi.org/10.1016/j.brainres.2016.08.032>.
- 943 94. Feingold, K.R. (2000). The Effect of Diet on Cardiovascular Disease and Lipid and
944 Lipoprotein Levels. In, K. R. Feingold, B. Anawalt, M. R. Blackman, A. Boyce, G.
945 Chrousos, E. Corpas, W. W. de Herder, K. Dhatariya, K. Dungan, J. Hofland, et al., eds.
- 946 95. Satoh, N., Shimatsu, A., Kotani, K., Sakane, N., Yamada, K., Suganami, T., Kuzuya, H., and
947 Ogawa, Y. (2007). Purified eicosapentaenoic acid reduces small dense LDL, remnant
948 lipoprotein particles, and C-reactive protein in metabolic syndrome. *Diabetes Care* *30*, 144–
949 146. <https://doi.org/10.2337/dc06-1179>.
- 950 96. Belchior, T., Paschoal, V.A., Magdalon, J., Chimin, P., Farias, T.M., Chaves-Filho, A.B.,
951 Gorjão, R., St-Pierre, P., Miyamoto, S., Kang, J.X., et al. (2015). Omega-3 fatty acids protect
952 from diet-induced obesity, glucose intolerance, and adipose tissue inflammation through
953 PPAR γ -dependent and PPAR γ -independent actions. *Mol. Nutr. Food Res.* *59*, 957–967.
954 <https://doi.org/10.1002/mnfr.201400914>.
- 955 97. Wang, Y., Wang, Y., Shehzad, Q., Su, Y., Xu, L., Yu, L., Zeng, W., Fang, Z., Wu, G., Wei,
956 W., et al. Does omega-3 PUFAs supplementation improve metabolic syndrome and related
957 cardiovascular diseases? A systematic review and meta-analysis of randomized controlled
958 trials. *Crit. Rev. Food Sci. Nutr.*, 1–28. <https://doi.org/10.1080/10408398.2023.2212817>.
- 959 98. Brady, L.M., Williams, C.M., and Lovegrove, J.A. (2004). Dietary PUFA and the metabolic
960 syndrome in Indian Asians living in the UK. *Proc. Nutr. Soc.* *63*, 115–125.
961 <https://doi.org/10.1079/pns2003318>.
- 962 99. Simão, A.N.C., Godeny, P., Lozovoy, M.A.B., Dichi, J.B., and Dichi, I. (2010). [Effect of n-
963 3 fatty acids in glycemic and lipid profiles, oxidative stress and total antioxidant capacity in
964 patients with the metabolic syndrome]. *Arq. Bras. Endocrinol. Metabol.* *54*, 463–469.
965 <https://doi.org/10.1590/s0004-27302010000500006>.
- 966 100. Mori, T.A., Burke, V., Puddey, I.B., Watts, G.F., O’Neal, D.N., Best, J.D., and Beilin, L.J.
967 (2000). Purified eicosapentaenoic and docosahexaenoic acids have differential effects on
968 serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly
969 hyperlipidemic men. *Am. J. Clin. Nutr.* *71*, 1085–1094.
970 <https://doi.org/10.1093/ajcn/71.5.1085>.
- 971 101. Woodman, R.J., Mori, T.A., Burke, V., Puddey, I.B., Watts, G.F., and Beilin, L.J. (2002).
972 Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood
973 pressure, and serum lipids in type 2 diabetic patients with treated hypertension. *Am. J. Clin.*
974 *Nutr.* *76*, 1007–1015. <https://doi.org/10.1093/ajcn/76.5.1007>.
- 975 102. Ogawa, A., Suzuki, Y., Aoyama, T., and Takeuchi, H. (2009). Dietary alpha-linolenic acid
976 inhibits angiotensin-converting enzyme activity and mRNA expression levels in the aorta of
977 spontaneously hypertensive rats. *J. Oleo Sci.* *58*, 355–360.
978 <https://doi.org/10.5650/jos.58.355>.
- 979 103. Liu, Y.X., Yu, J.H., Sun, J.H., Ma, W.Q., Wang, J.J., and Sun, G.J. (2023). Effects of
980 Omega-3 Fatty Acids Supplementation on Serum Lipid Profile and Blood Pressure in
981 Patients with Metabolic Syndrome: A Systematic Review and Meta-Analysis of Randomized

- 982 Controlled Trials. *Foods* 12. <https://doi.org/10.3390/foods12040725>.
- 983 104. Moore, K., Hughes, C.F., Ward, M., Hoey, L., and McNulty, H. (2018). Diet, nutrition and
984 the ageing brain: Current evidence and new directions. *Proc. Nutr. Soc.* 77, 152–163.
985 <https://doi.org/10.1017/S0029665117004177>.
- 986 105. Grosso, G., Galvano, F., Marventano, S., Malaguarnera, M., Bucolo, C., Drago, F., and
987 Caraci, F. (2014). Omega-3 fatty acids and depression: Scientific evidence and biological
988 mechanisms. *Oxid. Med. Cell. Longev.* 2014. <https://doi.org/10.1155/2014/313570>.
- 989 106. Mohajeri, M.H., Troesch, B., and Weber, P. (2015). Inadequate supply of vitamins and DHA
990 in the elderly: Implications for brain aging and Alzheimer-type dementia. *Nutrition* 31, 261–
991 275. <https://doi.org/10.1016/j.nut.2014.06.016>.
- 992 107. Cardoso, C., Afonso, C., and Bandarra, N.M. (2016). Dietary DHA and health: Cognitive
993 function ageing. *Nutr. Res. Rev.* 29, 281–294. <https://doi.org/10.1017/S0954422416000184>.
- 994 108. Yehuda, S., Rabinovitz, S., Carasso, R.L., and Mostofsky, D.I. (2002). The role of
995 polyunsaturated fatty acids in restoring the aging neuronal membrane. *Neurobiol. Aging* 23,
996 843–853. [https://doi.org/10.1016/s0197-4580\(02\)00074-x](https://doi.org/10.1016/s0197-4580(02)00074-x).
- 997 109. Serini, S., and Calviello, G. (2015). Reduction of Oxidative/Nitrosative Stress in Brain and
998 its Involvement in the Neuroprotective Effect of n-3 PUFA in Alzheimer's Disease. *Curr.*
999 *Alzheimer Res.* 13, 123–134. <https://doi.org/10.2174/1567205012666150921101147>.
- 1000 110. Freund-Levi, Y., Eriksdotter-Jönhagen, M., Cederholm, T., Basun, H., Faxén-Irving, G.,
1001 Garlind, A., Vedin, I., Vessby, B., Wahlund, L.O., and Palmblad, J. (2006). ω -3 fatty acid
1002 treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study - A
1003 randomized double-blind trial. *Arch. Neurol.* 63, 1402–1408.
1004 <https://doi.org/10.1001/archneur.63.10.1402>.
- 1005 111. Kotani, S., Sakaguchi, E., Warashina, S., Matsukawa, N., Ishikura, Y., Kiso, Y., Sakakibara,
1006 M., Yoshimoto, T., Guo, J., and Yamashima, T. (2006). Dietary supplementation of
1007 arachidonic and docosahexaenoic acids improves cognitive dysfunction. *Neurosci. Res.* 56,
1008 159–164. <https://doi.org/10.1016/j.neures.2006.06.010>.
- 1009 112. Lee, L.K., Shahar, S., Chin, A.V., and Yusoff, N.A.M. (2013). Docosahexaenoic acid-
1010 concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): A
1011 12-month randomised, double-blind, placebo-controlled trial. *Psychopharmacology (Berl)*.
1012 225, 605–612. <https://doi.org/10.1007/s00213-012-2848-0>.
- 1013 113. Sinn, N., Milte, C.M., Street, S.J., Buckley, J.D., Coates, A.M., Petkov, J., and Howe, P.R.C.
1014 (2012). Effects of n-3 fatty acids, EPA v. DHA, on depressive symptoms, quality of life,
1015 memory and executive function in older adults with mild cognitive impairment: A 6-month
1016 randomised controlled trial. *Br. J. Nutr.* 107, 1682–1693.
1017 <https://doi.org/10.1017/S0007114511004788>.
- 1018 114. Solfrizzi, V., Colacicco, A.M., D'Introno, A., Capurso, C., Parigi, A. Del, Capurso, S.A.,
1019 Argentieri, G., Capurso, A., and Panza, F. (2006). Dietary fatty acids intakes and rate of mild
1020 cognitive impairment. The Italian Longitudinal Study on Aging. *Exp. Gerontol.* 41, 619–627.
1021 <https://doi.org/10.1016/j.exger.2006.03.017>.
- 1022 115. Mazereeuw, G., Lanctôt, K.L., Chau, S.A., Swardfager, W., and Herrmann, N. (2012).
1023 Effects of omega-3 fatty acids on cognitive performance: A meta-analysis. *Neurobiol. Aging*
1024 33, 1482.e17-1482.e29. <https://doi.org/10.1016/j.neurobiolaging.2011.12.014>.

- 1025 116. Chen, K.H.M., Chuah, L.Y.M., Sim, S.K.Y., and Chee, M.W.L. (2010). Hippocampal
1026 region-specific contributions to memory performance in normal elderly. *Brain Cogn.* 72,
1027 400–407. <https://doi.org/https://doi.org/10.1016/j.bandc.2009.11.007>.
- 1028 117. Lee, L.K., Shahar, S., Rajab, N., Yusoff, N.A.M., Jamal, R.A., and Then, S.M. (2013). The
1029 role of long chain omega-3 polyunsaturated fatty acids in reducing lipid peroxidation among
1030 elderly patients with mild cognitive impairment: a case-control study. *J. Nutr. Biochem.* 24,
1031 803–808. <https://doi.org/https://doi.org/10.1016/j.jnutbio.2012.04.014>.
- 1032 118. Janssen, C.I.F., and Kiliaan, A.J. (2014). Long-chain polyunsaturated fatty acids (LCPUFA)
1033 from genesis to senescence: The influence of LCPUFA on neural development, aging, and
1034 neurodegeneration. *Prog. Lipid Res.* 53, 1–17. <https://doi.org/10.1016/j.plipres.2013.10.002>.
- 1035 119. Guo, Y.R., Lee, H.C., Lo, Y.C., Yu, S.C., and Huang, S.Y. (2018). N-3 polyunsaturated fatty
1036 acids prevent d-galactose-induced cognitive deficits in prediabetic rats. *Food Funct.* 9, 2228–
1037 2239. <https://doi.org/10.1039/c8fo00074c>.
- 1038 120. Dangour, A.D., Allen, E., Elbourne, D., Fasey, N., Fletcher, A.E., Hardy, P., Holder, G.E.,
1039 Knight, R., Letley, L., Richards, M., et al. (2010). Effect of 2-y n-3 long-chain
1040 polyunsaturated fatty acid supplementation on cognitive function in older people: A
1041 randomized, double-blind, controlled trial. *Am. J. Clin. Nutr.* 91, 1725–1732.
1042 <https://doi.org/10.3945/ajcn.2009.29121>.
- 1043 121. Johnson, E.J., McDonald, K., Caldarella, S.M., Chung, H.Y., Troen, A.M., and Snodderly,
1044 D.M. (2008). Cognitive findings of an exploratory trial of docosahexaenoic acid and lutein
1045 supplementation in older women. *Nutr. Neurosci.* 11, 75–83.
1046 <https://doi.org/10.1179/147683008X301450>.
- 1047 122. Van De Rest, O., Geleijnse, J.M., Kok, F.J., Van Staveren, W.A., Dullemeijer, C.,
1048 OldeRikkert, M.G.M., Beekman, A.T.F., and De Groot, C.P.G.M. (2008). Effect of fish oil
1049 on cognitive performance in older subjects: A randomized, controlled trial. *Neurology* 71,
1050 430–438. <https://doi.org/10.1212/01.wnl.0000324268.45138.86>.
- 1051 123. Aung, T., Halsey, J., Kromhout, D., Gerstein, H.C., Marchioli, R., Tavazzi, L., Geleijnse,
1052 J.M., Rauch, B., Ness, A., Galan, P., et al. (2018). Associations of omega-3 fatty acid
1053 supplement use with cardiovascular disease risks meta-analysis of 10 trials involving 77 917
1054 individuals. *JAMA Cardiol.* 3, 225–234. <https://doi.org/10.1001/jamacardio.2017.5205>.
- 1055 124. Den H, Dong X, Chen M, and Zou Z (2020). Efficacy of probiotics on cognition, and
1056 biomarkers of inflammation. *Aging (Albany NY)* 12, 4010–4039.
- 1057 125. Kassaian, N., Feizi, A., Aminorroaya, A., and Amini, M. (2019). Probiotic and synbiotic
1058 supplementation could improve metabolic syndrome in prediabetic adults: A randomized
1059 controlled trial. *Diabetes Metab. Syndr. Clin. Res. Rev.* 13, 2991–2996.
1060 <https://doi.org/10.1016/j.dsx.2018.07.016>.
- 1061 126. Bischof, G.N., and Park, D.C. (2015). Obesity and Aging: Consequences for Cognition,
1062 Brain Structure, and Brain Function. *Psychosom. Med.* 77, 697–709.
1063 <https://doi.org/10.1097/PSY.0000000000000212>.
- 1064 127. Pražnikar, Z.J., Kenig, S., Vardjan, T., Bizjak, M.Č., and Petelin, A. (2020). Effects of kefir
1065 or milk supplementation on zonulin in overweight subjects. *J. Dairy Sci.* 103, 3961–3970.
1066 <https://doi.org/10.3168/jds.2019-17696>.
- 1067 128. Cicero, A.F.G., Fogacci, F., Bove, M., Giovannini, M., and Borghi, C. (2021). Impact of a
1068 short-term synbiotic supplementation on metabolic syndrome and systemic inflammation in

- 1069 elderly patients: a randomized placebo-controlled clinical trial. *Eur. J. Nutr.* *60*, 655–663.
1070 <https://doi.org/10.1007/s00394-020-02271-8>.
- 1071 129. Guo, Z., Liu, X.M., Zhang, Q.X., Shen, Z., Tian, F.W., Zhang, H., Sun, Z.H., Zhang, H.P.,
1072 and Chen, W. (2011). Influence of consumption of probiotics on the plasma lipid profile: A
1073 meta-analysis of randomised controlled trials. *Nutr. Metab. Cardiovasc. Dis.* *21*, 844–850.
1074 <https://doi.org/10.1016/j.numecd.2011.04.008>.
- 1075 130. Papadakis GZ, Millo C, S.C., and Y Subramani, M. Singh, J.Wong, A.Kushida, A Malhotra,
1076 F.C. (2011). 乳鼠心肌提取 HHS Public Access. *Physiol. Behav.* *176*, 139–148.
1077 <https://doi.org/10.1016/j.clinthera.2015.04.002>.Gut-microbiota-brain.
- 1078 131. Bekkering, P., Jafri, I., Van Overveld, F.J., and Rijkers, G.T. (2013). The intricate
1079 association between gut microbiota and development of Type 1, Type 2 and Type 3 diabetes.
1080 *Expert Rev. Clin. Immunol.* *9*, 1031–1041. <https://doi.org/10.1586/1744666X.2013.848793>.
- 1081 132. Bostanciklioglu, M. (2019). The role of gut microbiota in pathogenesis of Alzheimer’s
1082 disease. *J. Appl. Microbiol.* *127*, 954–967. <https://doi.org/10.1111/jam.14264>.
- 1083 133. Sakurai, K., Toshimitsu, T., Okada, E., Anzai, S., Shiraishi, I., Inamura, N., Kobayashi, S.,
1084 Sashihara, T., and Hisatsune, T. (2022). Effects of Lactiplantibacillus plantarum OLL2712
1085 on Memory Function in Older Adults with Declining Memory: A Randomized Placebo-
1086 Controlled Trial. *Nutrients* *14*. <https://doi.org/10.3390/nu14204300>.
- 1087 134. Hwang, Y.H., Park, S., Paik, J.W., Chae, S.W., Kim, D.H., Jeong, D.G., Ha, E., Kim, M.,
1088 Hong, G., Park, S.H., et al. (2019). Efficacy and safety of lactobacillus plantarum C29-
1089 fermented soybean (DW2009) in individuals with mild cognitive impairment: A 12-week,
1090 multi-center, randomized, double-blind, placebo-controlled clinical trial. *Nutrients* *11*.
1091 <https://doi.org/10.3390/nu11020305>.
- 1092 135. Abdelhamid, M., Zhou, C., Jung, C.G., and Michikawa, M. (2022). Probiotic
1093 Bifidobacterium breve MCC1274 Mitigates Alzheimer’s Disease-Related Pathologies in
1094 Wild-Type Mice. *Nutrients* *14*. <https://doi.org/10.3390/nu14122543>.
- 1095 136. Zhu, G., Zhao, J., Zhang, H., Chen, W., and Wang, G. (2021). Administration of
1096 bifidobacterium breve improves the brain function of aβ1-42-treated mice via the modulation
1097 of the gut microbiome. *Nutrients* *13*. <https://doi.org/10.3390/nu13051602>.
- 1098 137. Asaoka, D., Xiao, J., Takeda, T., Yanagisawa, N., Yamazaki, T., Matsubara, Y., Sugiyama,
1099 H., Endo, N., Higa, M., Kasanuki, K., et al. (2022). Effect of Probiotic Bifidobacterium breve
1100 in Improving Cognitive Function and Preventing Brain Atrophy in Older Patients with
1101 Suspected Mild Cognitive Impairment: Results of a 24-Week Randomized, Double-Blind,
1102 Placebo-Controlled Trial. *J. Alzheimer’s Dis.* *88*, 75–95. <https://doi.org/10.3233/JAD-220148>.
- 1104 138. Xiao, J., Katsumata, N., Bernier, F., Ohno, K., Yamauchi, Y., Odamaki, T., Yoshikawa, K.,
1105 Ito, K., and Kaneko, T. (2020). Probiotic Bifidobacterium breve in Improving Cognitive
1106 Functions of Older Adults with Suspected Mild Cognitive Impairment: A Randomized,
1107 Double-Blind, Placebo-Controlled Trial. *J. Alzheimer’s Dis.* *77*, 139–147.
1108 <https://doi.org/10.3233/JAD-200488>.
- 1109 139. Bernier, F., Ohno, K., Katsumata, N., Shimizu, T., and Xiao, J. (2021). Association of
1110 Plasma Hemoglobin A1c with Improvement of Cognitive Functions by Probiotic
1111 Bifidobacterium breve Supplementation in Healthy Adults with Mild Cognitive Impairment.
1112 *J. Alzheimer’s Dis.* *81*, 493–497. <https://doi.org/10.3233/jad-201488>.

- 1113 140. Kobayashi, Y., Kuhara, T., Oki, M., and Xiao, J.Z. (2019). Effects of bifidobacterium breve
 1114 a1 on the cognitive function of older adults with memory complaints: A randomised, double-
 1115 blind, placebo-controlled trial. *Benef. Microbes* *10*, 511–520.
 1116 <https://doi.org/10.3920/BM2018.0170>.
- 1117 141. Kobayashi, Y., Kinoshita, T., Matsumoto, A., Yoshino, K., Saito, I., and Xiao, J.Z. (2019).
 1118 Bifidobacterium Breve A1 Supplementation Improved Cognitive Decline in Older Adults
 1119 with Mild Cognitive Impairment: An Open-Label, Single-Arm Study. *J. Prev. Alzheimer's*
 1120 *Dis.* *6*, 70–75. <https://doi.org/10.14283/jpad.2018.32>.
- 1121 142. Gillette-Guyonnet, S., Secher, M., and Vellas, B. (2013). Nutrition and neurodegeneration:
 1122 Epidemiological evidence and challenges for future research. *Br. J. Clin. Pharmacol.* *75*,
 1123 738–755. <https://doi.org/10.1111/bcp.12058>.
- 1124 143. Kinney, J.W., Bemiller, S.M., Murtishaw, A.S., Leisgang, A.M., Salazar, A.M., and Lamb,
 1125 B.T. (2018). Inflammation as a central mechanism in Alzheimer's disease. *Alzheimer's*
 1126 *Dement. Transl. Res. Clin. Interv.* *4*, 575–590. <https://doi.org/10.1016/j.trci.2018.06.014>.
- 1127 144. Hammond, T.R., Marsh, S.E., and Stevens, B. (2019). Immune Signaling in
 1128 Neurodegeneration. *Immunity* *50*, 955–974. <https://doi.org/10.1016/j.immuni.2019.03.016>.
- 1129 145. Zhang, W., Xiao, D., Mao, Q., and Xia, H. (2023). Role of neuroinflammation in
 1130 neurodegeneration development. *Signal Transduct. Target. Ther.* *8*, 267.
 1131 <https://doi.org/10.1038/s41392-023-01486-5>.
- 1132 146. Zhang, J., He, Z., Liu, L., Li, H., Wang, T., Zhu, X., Wang, Y., Zhu, D., Ning, Y., and Xu, Y.
 1133 (2023). Probiotic has prophylactic effect on spatial memory deficits by modulating gut
 1134 microbiota characterized by the inhibitory growth of *Escherichia coli*. *Front. Integr.*
 1135 *Neurosci.* *17*. <https://doi.org/10.3389/fnint.2023.1090294>.
- 1136 147. Iwasaki, M., Kanehara, R., Yamaji, T., Katagiri, R., Mutoh, M., Tsunematsu, Y., Sato, M.,
 1137 Watanabe, K., Hosomi, K., Kakugawa, Y., et al. (2022). Association of *Escherichia coli*
 1138 containing polyketide synthase in the gut microbiota with colorectal neoplasia in Japan.
 1139 *Cancer Sci.* *113*, 277–286. <https://doi.org/10.1111/cas.15196>.
- 1140 148. Huang, Y.H., Tain, Y.L., and Hsu, C.N. (2022). Maternal Supplementation of Probiotics,
 1141 Prebiotics or Postbiotics to Prevent Offspring Metabolic Syndrome: The Gap between
 1142 Preclinical Results and Clinical Translation. *Int. J. Mol. Sci.* *23*.
 1143 <https://doi.org/10.3390/ijms231710173>.
- 1144 149. Hsu, C.N., Hou, C.Y., Hsu, W.H., and Tain, Y.L. (2021). Early-life origins of metabolic
 1145 syndrome: Mechanisms and preventive aspects. *Int. J. Mol. Sci.* *22*.
 1146 <https://doi.org/10.3390/ijms222111872>.
- 1147 150. Hsu, C.N., Hou, C.Y., Hsu, W.H., and Tain, Y.L. (2021). Cardiovascular diseases of
 1148 developmental origins: Preventive aspects of gut microbiota-targeted therapy. *Nutrients* *13*.
 1149 <https://doi.org/10.3390/nu13072290>.
- 1150 151. Davari, S., Talaei, S.A., Alaei, H., and Salami, M. (2013). Probiotics treatment improves
 1151 diabetes-induced impairment of synaptic activity and cognitive function: Behavioral and
 1152 electrophysiological proofs for microbiome-gut-brain axis. *Neuroscience* *240*, 287–296.
 1153 <https://doi.org/10.1016/j.neuroscience.2013.02.055>.
- 1154 152. Mo, S.J., Lee, K., Hong, H.J., Hong, D.K., Jung, S.H., Park, S.D., Shim, J.J., and Lee, J.L.
 1155 (2022). Effects of *Lactobacillus curvatus* HY7601 and *Lactobacillus plantarum* KY1032 on
 1156 Overweight and the Gut Microbiota in Humans: Randomized, Double-Blinded,

1157 Placebo-Controlled Clinical Trial. *Nutrients* 14. <https://doi.org/10.3390/nu14122484>.

1158

1159 **Table 1**

Active ingredient	Mostly anti-inflammatory	Mostly antioxidant	Both properties	Actions
Resveratrol			x	Upregulating AMP-activated protein kinase. Increase endothelial nitric oxide bioavailability. inhibition of COX-2, 5-lipoxygenase, and nuclear factor- κ B. upregulation of IL-10 and the downregulation of interferon- γ and IL-17.
Tocotrienols (T3) and Tocopherols (TF)	x		x	Suppressing M1 macrophage differentiation. Increase NGF levels. \downarrow of the glutathione redox ratio and plasma lipid peroxidation. Vasorelaxation by stimulation of K-Ca channel
PUFAs	x			Downregulation of IL-6, tumor necrosis factor alpha (TNF- α), CRP, and IL-1 levels. Converting the phenotype of microglial cells from macrophage M1 state to an M2 state.
Probiotics	x			High IL-10-inducing activity in immune cells. Downregulation of hs-CRP and TNF- α levels

1160 Table 1 is a classification of the studied compounds according to their properties.

1161

1162 **Table 2**

1163

1164 Vitamin E on MetS

Efficacy	Action	ref
Potentially useful	Reduces levels of proinflammatory cytokines. Reduces M1 macrophage differentiation. Improves glucose tolerance and insulin sensitivity	(Zhao et al., 2015) [38]
Potentially useful	decreases plasma catecholamine concentrations, HOMA index and HbA1c values	(Manzella et al., 2001) [40]
Potentially useful	influences pancreatic islet function	(Asayama et al., 1986) [45]
Potentially useful	Positive impact on body weight	(Wong et al., 2017) [37]
Potentially useful	lowering total cholesterol, LDL-C, apoB, TG, FBG, and glucagon levels	(Qureshi et al., 2001) [66]
Potentially	Anti-hypertensive effect	(Aminuddin et al.,

useful		2021) [47]
Not Useful	Anti-hypertensive effect	(Palumbo et al., 2000) [50]

1165 Vitamin E on MCI

Efficacy	Action	ref
Potentially useful	up- or down-regulating some genes involved in the pathogenesis of neurodegeneration	(Gugliandolo et al., 2017) [54]
Potentially useful	Increases expression of NGF	(Rota et al., 2005) [57]
Potentially useful	Delay loss of cognition	(Maxwell et al., 2005) [61]
Not Useful	Delay loss of cognition	(Lloret et al., 2009) [35]
Not Useful	Delay loss of cognition	(Morris et al., 2015) [62]
Not Useful	Delay loss of cognition	(Jae et al., 2006) [63]

1166

1167 RVS on MetS

Efficacy	Action	ref
Potentially useful	Positive impact on insulin resistance and pancreatic beta-cells by the upregulation of AMP-activated protein kinase	(Szkudelski & Szkudelska, 2015) [74]
Potentially useful	Upregulation of lipolysis and reduction of lipogenesis in mature adipocytes	(Baile et al., 2011) [75]
Potentially useful	Increase endothelial NO bioavailability, modulation of the renin-angiotensin system	(Kim et al., 2018) [77]
Potentially useful	Glycemic control and insulin sensitivity, along with a reduction in serum levels of inflammatory markers	(Timmers et al., 2011) [90]
Not Useful	Increasing HDL-C level, decreasing BMI, TG and FBG	(Asgary et al., 2019) [79]

1168 RVS on MCI

Efficacy	Action	ref
Potentially useful	Neuroprotective effect by upregulation of neurogenesis and microvasculature, downregulation of astrocyte hypertrophy and microglial activation in the hippocampus	(Zhou et al., 2021) [81]
Potentially useful	improvement in spatial and emotional learning memory	(Gomez et al., 2016) [92]
Potentially useful	vasorelaxation by stimulation of K-Ca channel	(Li et al., 2000) [84]
Potentially	improvement in verbal memory performance by increasing	(Veronica Witte

useful	functional connectivity of the hippocampus and reduction of glucotoxicity in brain tissue	et al., 2014) [85]
---------------	---	--------------------

1169

1170

1171

PUFAs on MetS

Efficacy	Action	ref
Potentially useful	effect on BP and inflammatory markers such as IL-6, TNF- α , CRP, and IL-1 levels	(Wang et al., n.d.) [97]
Potentially useful	FBG control by insulin sensitivity, BP	(Liu et al., 2023) [103]
Potentially useful	FBG control	(Belchior et al., 2015) [96]
Potentially useful	Reduction the levels of brain receptor for advanced 14 glycation end-product and plasma TNF- α	(Y. R. Guo et al., 2018) [119]
Not Useful	FBG control	(Simão et al., 2010) [99]
Not Useful	FBG control	(Mori et al., 2000) [100]

1172

PUFAs on MCI

Efficacy	Action	ref
Potentially useful	Modulation of the production of inflammatory cytokines. Upregulation of antioxidant proteins, conversion of microglia cell phenotype from macrophage M1 state to an M2 state	(Serini & Calviello, 2015) [109]
Potentially useful	Impact on MMSE	(Freund-Levi et al., 2006) [110]
Potentially useful	Impact on MMSE	(Lee, Shahar, Rajab, et al., 2013b) [112,]
Potentially useful	Impact on MMSE	(Sinn et al., 2012) [113]
Potentially useful	Impact on MMSE	(Mazereeuw et al., 2012) [115]
Not Useful	Impact on MMSE	(Solfrizzi et al., 2006) [114]

1173

1174

Probiotics on MetS

Efficacy	Action	ref
Potentially useful	Improvement in waist circumference and in fasting plasma FBI, lipidic profile	(Cicero et al., 2021) [128]
Potentially useful	Significantly lower total cholesterol and LDL-C	(Z. Guo et al., 2011) [129]

Not Useful	Impact on HDL-C and triglycerides	(Z. Guo et al., 2011) [129]
-------------------	-----------------------------------	-----------------------------

1175

1176

Probiotics on MCI

Efficacy	Action	ref
Potentially useful	Improvement in cognitive function associated with lower level of MDA and hs-CRP	(Den H et al., 2020) [124]
Potentially useful	Suppressed brain atrophy progression	(Asaoka et al., 2022) [137]
Potentially useful	Suppressed the hippocampal expressions of inflammation	(Xiao et al., 2020) [138]
Potentially useful	Improvement of cognitive functions as measured with RBANS total score associated with HbA1c reduction	(Bernier et al., 2021) [139]
Potentially useful	Visual memory: gut microbiota, supposed correlation with blood ammonia levels and IL-1 activity	(Sakurai et al., 2022) [133]
Not Useful	No differences observed in "immediate memory	(Kobayashi et al., 2019) [141]

1177

1178

1179

1180

1181

1182

1183

1184

1185

1186

1187

1188

Table 2 offers a view of the proposed mechanism by which some nutraceuticals may have a positive impact on Mets and MCI. It summarizes the nutraceuticals selected in this review and offers a schematic representation of possible implications for clinical practice.

BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; FBG, fasting blood glucose; FBI, fasting blood insulin; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of insulin resistance; IL-1, Interleukin 1; IL-6, Interleukin 6; LDL-C, low-density lipoprotein; NGF, the nerve growth factor; NO, Nitric oxide; TNF- α , Tumour Necrosis Factor alpha.

Highlights

- Metabolic Syndrome and Mild Cognitive Impairment are interconnected by common inflammatory pathways.
- No codified medical treatment is available for halting or slowing their progression.
- Our aim was to review evidence on nutraceuticals used in these conditions.
- Some nutraceuticals are effective on both, others showed contrasting results.