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Potential benefits of phytochemicals against Alzheimer's disease

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Manuscripts

1 **Potential benefits of phytochemicals against Alzheimer's disease**

2

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Abstract

Our current therapeutic drugs for Alzheimer's disease (AD) are predominantly derived from the alkaloid class of plant phytochemicals. These drugs, such as Galantamine and Rivastigmine, attenuate the decline in the cholinergic system but, as the alkaloids occupy the most dangerous end of the phytochemical spectrum (indeed they function as feeding deterrents and poisons to other organisms within the plant itself), they are often associated with unpleasant side effects. In addition, these cholinesterase inhibiting alkaloids target only 1 system in a disorder which is typified by multifactorial deficits. The more benign terpene (such as Ginkgo biloba, Ginseng, Melissa Officinalis (Lemon balm) and Salvia lavandulaefolia (sage)) and phenolic (such as Resveratrol) phytochemicals arguably offer a safer alternative and, as well as demonstrating efficacy in cholinesterase inhibition, these phytochemicals are able to target other salient systems; such as cerebral blood flow, free radical scavenging, anti-inflammation, inhibition of amyloid- β neurotoxicity, glucoregulation and interaction with other neurotransmitters (such as GABA) and signalling pathways (e.g. via kinase enzymes).

51 1. Background

52 The Brain Performance and Nutrition Research Centre (BPNRC) has, over the past decade or
53 so, investigated the cognitive and physical effects of over 20 essential nutrients and plant
54 secondary metabolites (phytochemicals) in healthy adults and children. The premise
55 underlying this body of research is that the supplementation of these compounds will, via a
56 multitude of mechanisms, enhance some aspect/s of cognitive function, mood and/or physical
57 performance. Naturally these studies produce varied results with some robust results evinced
58 from compounds such as caffeine⁽¹⁾, the neural substrates oxygen^(2; 3) and glucose⁽⁴⁾ and, more
59 recently, supplementation of the water soluble vitamins⁽⁵⁾. However, other supplemented
60 compounds appear almost to elicit no cognitive benefit to the young, healthy cohorts utilized;
61 the polyphenol resveratrol, for example^(6; 7; 8). This has led to the conclusion that some
62 supplements may have limited cognitive benefit in those who are within the cognitive peak
63 age-range (i.e. 18-35yrs)⁽⁹⁾ and that the mechanism underpinning their purported activity
64 might be of more interest and benefit to those who are experiencing natural and pathological
65 neurocognitive decline. Currently, pharmacological treatment options for pathological
66 neurocognitive disorders like Alzheimer's disease (AD) are derived from the alkaloid class of
67 plant phytochemical compounds and this report will outline the disadvantages of this group
68 and present an argument for, instead, looking at the potential benefit that taking these drugs
69 from the more benign terpene and phenolic class of phytochemicals could provide in terms of
70 safety and clinical benefit.

71

72 2. Alzheimer's disease and current treatment options from the alkaloid secondary
73 metabolites

74 AD is the most common form of dementia; a global, progressive neurocognitive disorder
75 typified by amyloid- β protein plaques outside of; and tau protein tangles inside of, neural cell

76 bodies which ultimately disrupts all cognitive processes and results in death⁽¹⁰⁾. The World
77 Alzheimer Report 2015⁽¹¹⁾ estimates that, worldwide, 46.8 million people live with a
78 dementia and that this number will double every 20 years. The main risk factor for
79 developing AD, and other dementias, is age but this is a multifactorial disease which is also
80 influenced (positively and negatively) by genetics (specifically the APOE gene has received
81 much recent attention)⁽¹²⁾, diet⁽¹³⁾, nicotine^(14; 15) and alcohol⁽¹⁶⁾ consumption, free radical
82 damage⁽¹⁷⁾, glucose regulation⁽¹⁸⁾, cerebral blood flow⁽¹⁹⁾, inflammation⁽²⁰⁾, ferrous metals⁽²¹⁾,
83 hormones⁽²²⁾, socioeconomic status⁽²³⁾ and many more known and unknown variables.

84 The morphological changes to neurons that the above risk factors mediate are seen to
85 predominantly disrupt the cholinergic neurotransmitter system and, in turn, the cognitive
86 processes that the ubiquitous neurotransmitter acetylcholine sub-serves. Hence the
87 progressive, global deficits in cognitive function seen in AD and the rationale for the target of
88 current pharmaceutical drugs in attenuating this cholinergic decline⁽²⁴⁾. These drugs include
89 Galantamine and Rivastigmine and, as a group of drugs defined as cholinesterase inhibitors
90 (preventing the deamination of acetylcholine), these are currently the only approved first line
91 pharmacologic treatment for AD in the UK⁽²⁵⁾. A recent Cochrane review reported that these
92 drugs attenuate the decline in cognition, daily living and behaviour in AD when compared to
93 placebo⁽²⁶⁾ but, interestingly, highlighted that none of the treatment effects were large.
94 Cholinesterase drugs also lack efficacy in some stages of AD and here use of the
95 antipsychotic drug Risperidone is often turned to in order to mediate challenging
96 behaviour⁽²⁷⁾. Cholinesterase drugs are also associated with some quite unpleasant side effects
97 (including gastrointestinal problems⁽²⁶⁾) and this is likely related to their current derivation
98 from the alkaloid spectrum of plant secondary metabolites (hereafter referred to as
99 phytochemicals).

100 Phytochemicals exist to mediate communication and protection of the static plant and, in
101 doing so, increase its survivability⁽²⁸⁾. These compounds fall into 1 of 3 categories; the
102 alkaloids, terpenes and phenolics, with this order denoting their potency from dangerous to
103 relatively benign, and each category appears to have a particular function. Here the alkaloids
104 are broadly expressed to deter the encroachment of other plants and potentially destructive
105 insects. The terpenes also play a role in defence and deterrence but their provision of
106 attractive colours and smells within the plant also demonstrates their role in attraction to
107 facilitate pollination. Finally, the phenolics occupy the most benign ground in terms of safety
108 and their role appears to be one of protection; expressed as they are when the plant comes
109 under some kind of stress⁽²⁸⁾. Of interest here, many phenolic and terpene phytochemicals
110 have also demonstrated efficacy against cholinergic decline and, beyond this, many of the
111 other factors contributing to AD; which the current alkaloid-based drugs do not. Added to
112 this, their relatively benign ecological roles means that they may also represent a safer way of
113 attenuating neurocognitive decline in AD. The following discusses those terpenes and
114 phenolics which represent the current most promising phytochemicals in this regard.

115

116 3. The potential benefit of terpene phytochemicals against Alzheimer's disease

117 Terpenes are a diverse group of more than 30,000 lipid-soluble compounds and exhibit a
118 range of toxicity from deadly to entirely edible. This is in keeping with their broad range of
119 ecological roles which include antimicrobial properties and a range of measures which attract
120 symbiotes for the purposes of pollination, seed dispersal, and secondary protective roles. This
121 complex communication with insects requires the ability to interact directly with the central
122 nervous system (CNS) including hormones and the GABA and cholinergic neurotransmitter
123 systems; interactions which should also translate to the human CNS and, as a result, provide
124 benefit to AD^(28 for review).

125

126 3.1 Ginkgo biloba

127 Extracts of Ginkgo biloba leaf contain a number of bioactive components which include
128 diterpenes, ginkgolides A, B, C, J and M, the sesquiterpene bilobalide and a range of
129 flavonoids. The synergistic effects of these phytochemicals results in interactions with a
130 number of CNS systems which would be expected to attenuate neurocognitive decline. These
131 include an upregulation of the vasorelaxatory neurotransmitter nitric oxide (NO) and a
132 resulting increase in cerebral blood flow (CBF), a downregulation in the enzymatic
133 deamination of monoaminergic neurotransmitters, free radical scavenging and
134 neuroprotection which includes reduced amyloid- β neurotoxicity^(29; 30; 31). These interactions
135 support the prescription of Ginkgo for millennia in traditional Eastern forms of medicine for
136 disorders of old age; including AD⁽³²⁾ and the beneficial effects seen in modern controlled
137 intervention trials.

138 In 2002 a Cochrane review concluded that “overall there is promising evidence of
139 improvement in cognition and function associated with Ginkgo”⁽³³⁾ but, in 2009, this message
140 had changed to one blighted by “inconsistent” and “unconvincing” results⁽³⁴⁾. This is despite
141 a study conducted in the same year where cognitive decline, as assessed by the Alzheimer’s
142 disease assessment scale (ADAS-Cog), was attenuated by Ginkgo⁽³⁵⁾ but perhaps represents
143 the influence of several small, heterogeneous studies on a research area still in its infancy.
144 Nevertheless, since this review, a handful of larger scale reviews have reported more
145 promising results of Ginkgo. In 2010 a review of 9 studies, comprising 2372 patients with
146 various dementias, found that ginkgo attenuated declines in cognitive performance across all
147 dementia groups tested and additional improvements in activities of daily living were seen in
148 the AD groups⁽³⁶⁾. In the same year a review of 6 studies found that 6 months administration
149 of ginkgo resulted in significant improvements on the ADAS-cog⁽³⁷⁾. Importantly, this result

150 was evinced when baseline risk was taken into account and might represent an important
151 methodological consideration in AD research. In support of this, a separate review⁽³⁸⁾ found
152 that improvements seen in daily living, cognitive function and amelioration of
153 neuropsychiatric symptoms (such as psychosis, agitation, aggression, anxiety, euphoria/
154 dysphoria or disordered motor behaviour), in a review of 6 studies comprising 1800
155 participants with AD, were most striking in those suffering significant levels of
156 neuropsychiatric symptoms; thus individual differences in risk levels and severity of
157 symptoms likely has an impact on response to Ginkgo and overall study findings; especially
158 if small cohorts are utilized in individual trials.

159

160 3.2 Ginseng

161 Ginseng has a 5000yr history of medicinal consumption⁽³⁹⁾ and comprises 40 or more
162 bioactive saponins (known as ginsenosides) which exert anti-fungal/viral/bacterial/feeding
163 effects within the plant^(40; 41). Again, this terpene-derived nutritional supplement demonstrates
164 efficacy in interacting with numerous physiological systems, including acting as an
165 antioxidant, stimulating NO production and acting as a ligand for glucocorticoid and
166 androgen receptors; interactions which, among others, are seen to increase immune function,
167 enhance CNS function and prevent cardiovascular and other diseases in animal models⁽⁴²⁾.
168 Specific neurocognitive interactions with neurotransmitter function and the processes of
169 neurogenesis and long-term potentiation are also observed to exert anti-stress, antidepressant,
170 and anxiolytic effects, to moderate fatigue and improve memory in impaired rodents^(43; 44).

171 Research in young healthy participants is still in its infancy and buoyed by heterogeneous
172 methodology but, on the whole, provides promise in terms of cognitive enhancement^{(45; 46; 47;}
173 ⁴⁸⁾. *In vitro* and animal data supports the potential for ginseng to be of specific benefit to AD-
174 induced cognitive decline where ginsenosides have been observed to minimise the inhibitory

175 effect of amyloid- β protein on cholinergic transmission⁽⁴⁹⁾ and, in turn, prevent the resulting
176 amnesiac effects in rats⁽⁵⁰⁾. To the best of current knowledge, however, only 2 trials exist
177 which investigate whether these cognitive benefits also extend to AD in humans. The first of
178 these reports on the 12 week consumption of 9g/day Korean ginseng in 15 patients with
179 dementia where scores on the ADAS and clinical dementia rating (CDR) were significantly
180 improved⁽⁵¹⁾. The second trial is a follow-up of patients in this same trial after 24 weeks
181 where a significant improvement on the Korean Mini Mental State Exam (MMSE) was
182 evinced following 4.5- and 9g/day ginseng and maintained at 48 and 96 weeks⁽⁵²⁾.

183

184 3.3 Melissa Officinalis (Lemon balm)

185 Melissa is another terpene with a centuries-long history for treating disorders which modern
186 research has confirmed efficacy for; including as a memory and mood enhancer⁽⁵³⁾. The
187 bioactives underpinning these effects include monoterpenes and sesquiterpenes; which
188 include 1, 8 cineole⁽⁵⁴⁾, and the CNS-relevant effects of these compounds includes antioxidant
189 activity^(55; 56), activation of the cholinergic system (including cholinesterase inhibition)^{(55; 57;}
190 ^{58; 59)} and upregulation of GABAergic neurons⁽⁶⁰⁾.

191 These interactions would suggest benefit to AD sufferers and, indeed, 1 of the only 2
192 controlled trails which has investigated Melissa here observed reduced agitation and
193 improved cognitive (ADAS-cog) and behavioural function (as assessed by the Cognitive
194 Drug Research (CDR) test battery) following 16 weeks administration of an alcoholic-
195 Melissa tincture in a group of mild-moderate sufferers⁽⁶¹⁾. The other of the 2 studies,
196 however, failed to find statistically significant differences in AD symptoms with Melissa⁽⁶²⁾.
197 This study, though, administered Melissa in the form of an aromatherapy spray (dispersed
198 once in the am and pm in patient rooms), or essential oil hand massage (with a 3rd group
199 receiving a combination), which also contained lavender. This novel approach to

200 administration presents an unknown quantity in terms of subsequent plasma levels of Melissa
201 and time needed for the bioactives to reach the CNS and, as such, makes it difficult to
202 compare with the above study and related studies which administer phytochemicals orally. It
203 could also be the case that the alcoholic matrix in the initial study in some way enhanced, or
204 indeed was solely responsible for, the significant effects seen there. Nevertheless, it is
205 important to note that the latter study did observe clinical benefit to some participants and
206 this may indicate the very important role of individual differences in response to terpene
207 phytochemicals; a consideration also noted with Ginkgo studies above. Here too it may be the
208 case that pre-AD differences and current symptom severity influence the role that terpenes
209 play and, with the Melissa essential oil study specifically, it could be that the response to
210 scent (including lavender; which contains the active terpene linalool) and the pleasant
211 sensation of being massaged, interact to produce effects which are of benefit to some and not
212 others.

213

214 3.4 *Salvia Lavandulaefolia* and *Officinalis* (Sage)

215 Sage has a history stretching back as far as the ancient Greeks where it was used as a
216 cognitive enhancer and to prevent age-related decline; hence the derivation of the word sage
217 in relation to wisdom. The 2 most abundant bioactive monoterpenes in sage are 1, 8 cineole
218 and camphor and, of interest here, these monoterpenes have demonstrated potent
219 cholinesterase inhibiting properties^(63; 64; 65; 66); with 1, 8 cineole alone evincing the greatest
220 effects⁽⁶³⁾. These CNS effects produce enhanced secondary memory, accuracy and attention
221 in healthy aged (over 65yrs) participants⁽⁶⁷⁾ and consumption of this terpene, in the form of an
222 essential oil, is reportedly well tolerated in a small group (N=11) of patients aged 76-95yrs
223 with mild-moderate AD following 6 weeks of 50-150µl daily consumption of *salvia*
224 *officinalis* (SO)⁽⁶⁸⁾. The latter study didn't observe any statistically significant cognitive

225 benefit but this was not the *a priori* aim of the study and this is reflected in the sample size.
226 Nevertheless the authors do report ‘positive indications’ on the cognitive test battery used
227 (CDR) and this is in line with the only other trial investigating the benefit of sage in AD⁽⁶⁹⁾.
228 Here 19 participants (65-80yrs), with mild-moderate AD, consumed an SO-alcoholic tincture
229 for 16 weeks and better outcomes on the ADAS-cog, compared to the placebo controls, was
230 observed. This study also demonstrated a trend towards reduced agitation in the SO group.

231

232 4. The potential benefit of phenolic phytochemicals against Alzheimer’s disease
233 Currently ~10,000 compounds have been classified as polyphenols and this large class
234 comprises both flavonoid and non-flavonoid forms. The former comprise the largest grouping
235 and these can be further sub-divided into isoflavones (found in soy and soy products),
236 flavones (found, for example, in sweet pepper), flavanones (found in citrus fruits), flavanols
237 (which can be further sub-categorised into flavan-3-ols (found in tea) and proanthocyanidins
238 (found in fruits)), flavonols (fruits and vegetables; specifically onions) and anthocyanins
239 (specifically found in berries)⁽⁷⁰⁾.

240 Epidemiological data has established links between the consumption of polyphenol-rich diets,
241 and specific polyphenols, and reduced incidences of AD in human populations. Consumption
242 of fruits and vegetables and total levels of flavonoids are associated with protection against,
243 or slowed progression of, AD and other dementias^(71; 72; 73). Large cohort studies have also
244 evidenced links between neurocognitive protection (as indexed in all cases by scores on the
245 MMSE) and tea consumption in elderly cohorts^(74; 75) as well as chocolate and red-wine⁽⁷⁶⁾.

246

247 4.1 Resveratrol

248 Resveratrol derives from a sub-class of non-flavonoid polyphenols termed stilbenes and is
249 found in limited sources which include grapes and, as a result, wine. Resveratrol has received

250 much research attention regarding its potential to benefit a number of disease states;
251 including cardiovascular disease⁽⁷⁷⁾, cancer⁽⁷⁸⁾ and even life extension in a range of animal
252 models⁽⁷⁹⁾. The many and varied health effects attributed to resveratrol are likely underpinned
253 by the multifarious biological targets that it interacts with. These include, but are not limited
254 to, cyclooxygenase (COX) 1 and 2; hence the anti-inflammatory effects of resveratrol,
255 sirtuins and various kinases; enabling resveratrol to interact directly with cell signalling and
256 DNA/RNA and lipoproteins; explaining resveratrols link to cardiovascular health⁽⁸⁰⁾.
257 Interaction with these targets, and others like upregulation of CBF^(6; 7), and the ability of
258 resveratrol to attenuate amyloid- β induced cell death *in vitro*⁽⁸¹⁾, suggests that this polyphenol
259 should be capable of beneficial therapeutic potential in AD. Indeed, results from animal
260 models supports the function of resveratrol here with reduced markers of pathology, e.g.
261 amyloid- β plaques⁽⁸²⁾, and behavioural deficits, e.g. improved learning and memory⁽⁸³⁾, in
262 response to resveratrol exposure and consumption (25mg/kg/day) of resveratrol respectively.

263 However, to the best of current knowledge, only 1 study exists which investigates resveratrol
264 in human volunteers with AD. Here a phase-2 randomized, placebo-controlled, double-blind
265 12 month trial of 500mg/day (escalating to 1000mg x2 daily) resveratrol was conducted in
266 participants with mild-moderate AD⁽⁸⁴⁾. Unfortunately the therapeutic measures of this study
267 were limited and, whilst amyloid- β markers were reduced by resveratrol, this was not more
268 significant than in the placebo group, and brain volume loss was not attenuated. Resveratrol
269 consumption was generally well tolerated but participants did report significant
270 gastrointestinal problems and weight loss which is likely due to the high dose being received
271 after escalation as these side effects aren't seen often in the literature with doses at or lower
272 than 500mg.

273

274 **Conclusions**

275 This review began with the assertion that our current alkaloid-derived AD pharmaceutical
276 treatments, like Galantamine and Rivastigmine, produce unpleasant side effects and,
277 ultimately, target only 1 of the multifactorial deficits of this progressive neurocognitive
278 disorder. Whilst this sole target of attenuating cholinergic decline is arguably one, if not the,
279 most important and easily influenced today, it was argued here that the terpene and phenolic
280 groupings of plant phytochemicals might offer an equally efficacious and safer alternative for
281 AD drugs which target multiple deficits. The terpene and phenolic studies presented here are
282 few and a clear, overall view hindered by heterogeneous trials where sample size, method of
283 assessment, trial length, route of administration and individual differences associated with
284 pre-AD status and current severity of symptoms vary or are not considered. Another area
285 which future studies should focus, and something which resonated from several talks at the
286 Nutrition Society spring conference, is the concept of ‘responders’ and ‘non-responders’ in
287 phytochemical research. These terms refer to individuals who experience an anticipated
288 pharmacokinetic response to consumption of drugs, and those who don’t, respectively; with
289 this journey based on a whole host of known and unknown factors. This likely includes the
290 speed of gut transit, the microbiotic profile of the gastrointestinal tract and the functionality
291 of efflux pumps and these factors will be unique to each participant. It’s likely that the impact
292 of these individual differences will be diluted in large cohorts but, apart from the meta-
293 analyses discussed, one common factor across terpene and phenolic research trials is
294 relatively small sample sizes. Studies with these phytochemicals undoubtedly hold promise
295 but robust and replicable outcomes won’t be evinced until the above methodological
296 constraints are addressed.

297

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305

306 **Conflict of interest**

307 None

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