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Potential benefits of phytochemicals against Alzheimer's disease

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Our current therapeutic drugs for Alzheimer's disease 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 one system in a disorder, which is typified by multifactorial deficits. The present paper will look at the more benign terpene (such as *Ginkgo biloba*, Ginseng, *Melissa officinalis* (lemon balm) and *Salvia lavandulaefolia* (sage)) and phenolic (such as resveratrol) phytochemicals; arguing that they offer a safer alternative and that, 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 γ-aminobutyric acid) and signalling pathways (e.g. via kinase enzymes).

Alzheimer's disease: Phytochemicals: Alkaloid: Terpene: Phenolic

Background

To date, research into the psychophysiological effects of nutritional supplements in human subjects has predominantly focused on young, healthy, cognitively intact individuals. The premise underlying this body of research is that the supplementation of these compounds will, via a multitude of mechanisms, enhance some aspect/s of cognitive function, mood and/or physical performance. Naturally these studies produce varied results with some robust results evinced from compounds such as caffeine[1], the neural substrates oxygen[2,3] and glucose[4] and, more recently, supplementation of the water-soluble vitamins[5]. However, other supplemented compounds appear almost to elicit no cognitive benefit to the young, healthy cohorts utilised; the polyphenol resveratrol, for example[6–8]. This has led to the conclusion that some supplements may have limited cognitive benefit in those who are within the cognitive peak age-range (i.e. 18–35 years)[9] and that the mechanism underpinning their purported activity might be of more interest and benefit to those who are experiencing natural and pathological neurocognitive decline. Currently, pharmacological treatment options for pathological neurocognitive disorders such as Alzheimer's disease (AD) are derived from the alkaloid class of plant phytochemical compounds and this report will outline the disadvantages of this group and present an argument for, instead, looking at the potential benefit that taking these drugs from the more benign terpene and phenolic class of phytochemicals could provide in terms of safety and clinical benefit.

Alzheimer's disease and current treatment options from the alkaloid secondary metabolites

AD is the most common form of dementia. This is a global, progressive neurocognitive disorder typified by amyloid-β protein plaques and tau protein tangles outside and inside, respectively, of the neural cell body. These insults ultimately disrupt all cognitive processes

Abbreviations: AD, Alzheimer's disease; ADAS-cog, Alzheimer's disease assessment scale; CNS, central nervous system.

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and result in death[10]. The World Alzheimer Report 2015[11] estimates that, worldwide, 46·8 million people live with a dementia and that this number will double every 20 years. The main risk factor for developing AD, and other dementias, is age but this is a multifactorial disease, which is also influenced (positively and negatively) by genetics (specifically the ApoE gene has received much recent attention)[12], diet[13], nicotine[14,15] and alcohol[16] consumption, free radical damage[17], glucose regulation[18], cerebral blood flow[19], inflammation[20], ferrous metals[21], hormones[22], socioeconomic status[23] and many more known and unknown variables.

The morphological changes to neurons that the aforementioned risk factors mediate are seen to predominantly disrupt the cholinergic neurotransmitter system and, in turn, the cognitive processes that the ubiquitous neurotransmitter acetylcholine sub-serves. Hence, current pharmaceutical drugs for AD solely target this cholinergic decline[24]. These drugs include galantamine and rivastigmine and, as a group of drugs defined as cholinesterase inhibitors (preventing the deamination of acetylcholine), these are currently the only approved first line pharmacologic treatment for AD in the UK[25]. A recent Cochrane review reported that these drugs attenuate the decline in cognition, daily living and behaviour in AD when compared with placebo[26] but, interestingly, highlighted that none of the treatment effects were large. Cholinesterase inhibiting drugs also lack efficacy in some stages of AD and here use of the antipsychotic drug risperidone is often turned to in order the mediate challenging behaviour[27]. Cholinesterase drugs are also associated with some quite unpleasant side effects (including gastrointestinal problems[26]) and this is likely related to their current derivation from the alkaloid spectrum of plant secondary metabolites (hereafter referred to as phytochemicals) in that they occupy relatively more dangerous roles within the plant.

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

Potential benefit of terpene phytochemicals against Alzheimer's disease

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

Ginkgo biloba

Extracts of *G. biloba* leaf contain a number of bioactive components, which include diterpenes, ginkgolides A, B, C, J and M, the sesquiterpene bilobalide and a range of flavonoids. The synergistic effects of these phytochemicals results in interactions with a number of CNS systems, which would be expected to attenuate neurocognitive decline. These include an up-regulation of the vasorelaxatory neurotransmitter nitric oxide and a resulting increase in cerebral blood flow, a down-regulation in the enzymatic deamination of monoaminergic neurotransmitters, free radical scavenging and neuroprotection, which includes reduced amyloid-β neurotoxicity[29–31]. These interactions support the prescription of ginkgo for millennia in traditional Eastern forms of medicine for disorders of old age including AD[32] and the beneficial effects seen *in vitro* and *in vivo* animal models of AD; where attenuation of cognitive decline has been observed in the AD mouse[33]; often reported to be due to protection against amyloid-β-induced oxidative stress[34]. Modern, controlled intervention trials in human subjects have also yielded some positive results.

In 2002, a Cochrane review concluded that 'overall there is promising evidence of improvement in cognition and function associated with ginkgo'[35] but, in 2009, this message had changed to one blighted by 'inconsistent' and 'unconvincing' results[36]. This is despite a study conducted in the same year where cognitive decline, as assessed by the Alzheimer's disease assessment scale (ADAS-cog), was attenuated by ginkgo[37] but perhaps represents the influence of several small, heterogeneous studies on a research area still in its infancy. Nevertheless, since this review, a handful of larger scale reviews have reported more promising results of ginkgo. In 2010, a review of nine studies, comprising 2372 patients with various dementias, found that ginkgo attenuated declines in cognitive performance across all dementia groups tested and additional improvements in activities of daily living were seen in the AD groups[38].

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In the same year a review of six studies found that 6 months administration of ginkgo resulted in significant improvements on the ADAS-cog[39]. Importantly, this result was evinced when baseline risk was taken into account and might represent an important methodological consideration in AD research. In support of this, a separate review[40] found that improvements seen in daily living, cognitive function and amelioration of neuropsychiatric symptoms (such as psychosis, agitation, aggression, anxiety, euphoria/dysphoria or disordered motor behaviour), in a review of six studies comprising 1800 participants with AD, were most striking in those suffering significant levels of neuropsychiatric symptoms; thus individual differences in risk levels and severity of symptoms likely has an impact on response to ginkgo and overall study findings; especially if small cohorts are utilised in individual trials.

Ginseng

Ginseng has a 5000-year history of medicinal consumption[41] and comprises forty or more bioactive saponins (known as ginsenosides), which exert anti-fungal/viral/bacterial/feeding effects within the plant[42,43]. Again, this terpene-derived nutritional supplement demonstrates efficacy in interacting with numerous physiological systems, including acting as an antioxidant, stimulating nitric oxide production and acting as a ligand for glucocorticoid and androgen receptors; interactions which, among others, are seen to increase immune function, enhance CNS function and prevent CVD and other diseases in animal models[44]. Specific neurocognitive interactions with neurotransmitter function and the processes of neurogenesis and long-term potentiation are also observed to exert anti-stress, antidepressant, and anxiolytic effects, to moderate fatigue and improve memory in impaired rodents[45,46].

Research in young healthy participants is still in its infancy and buoyed by heterogeneous methodology but, on the whole, provides promise in terms of cognitive enhancement[47–50]. *In vitro* and animal data supports the potential for ginseng to be of specific benefit to AD-induced cognitive decline where ginsenosides have been observed to minimise the inhibitory effect of amyloid-β protein on cholinergic transmission[51] and, in turn, prevent the resulting amnesiac effects in rats[52]. To the best of current knowledge, however, only two trials exist, which investigate whether these cognitive benefits also extend to AD in human subjects. The first of these reports on the 12-week consumption of 9 g/d Korean ginseng in fifteen patients with dementia where scores on the ADAS-cog and clinical dementia rating were significantly improved[53]. The second trial is a follow-up of patients in this same trial after 24 weeks where a significant improvement on the Korean Mini Mental State Exam was evinced following 4·5 and 9 g/d ginseng and maintained at 48 and 96 weeks[54].

Melissa officinalis (lemon balm)

Melissa is another terpene with a centuries-long history for treating disorders, which modern research has confirmed efficacy for; including as a memory and mood enhancer[55]. The bioactives underpinning these effects include monoterpenes and sesquiterpenes; which include 1, 8 cineole[56], and the CNS-relevant effects of these compounds includes antioxidant activity[57,58], activation of the cholinergic system (including cholinesterase inhibition)[57,59–61] and up-regulation of γ-aminobutyric acid (GABA) ergic neurons[62].

These interactions would suggest benefit to AD sufferers and, indeed, one of the only two controlled trails, which has investigated Melissa here observed reduced agitation and improved cognitive (ADAS-cog) and behavioural function (as assessed by the Cognitive Drug Research test battery) following 16 weeks administration of an alcoholic-Melissa tincture in a group of mild–moderate sufferers[63]. The other of the two studies, however, failed to find statistically significant differences in AD symptoms with Melissa[64]. This study, though, administered Melissa in the form of an aromatherapy spray (dispersed once in the morning and afternoon in patient rooms) or essential oil hand massage (with a third group receiving a combination), which also contained lavender. This novel approach to administration presents an unknown quantity in terms of subsequent plasma levels of Melissa and time needed for the bioactives to reach the CNS and, as such, makes it difficult to compare with the above study and related studies, which administer phytochemicals orally. It could also be the case that the alcoholic matrix in the initial study in some way enhanced, or indeed was solely responsible for, the significant effects seen there. Nevertheless, it is important to note that the latter study did observe clinical benefit to some participants and this may indicate the very important role of individual differences in response to terpene phytochemicals; a consideration also noted with ginkgo studies described earlier. Here too it may be the case that pre-AD differences and current symptom severity influence the role that terpenes play and, with the Melissa essential oil study specifically, it could be that the response to scent (including lavender; which contains the active terpene linalool) and the pleasant sensation of being massaged, interact to produce effects which are of benefit to some and not others.

Salvia lavandulaefolia and Salvia officinalis (sage)

Sage has a history stretching back as far as the ancient Greeks where it was used as a cognitive enhancer and to prevent age-related decline; hence the derivation of the word sage in relation to wisdom. The two most abundant bioactive monoterpenes in sage are 1, 8 cineole and camphor and, of interest here, these monoterpenes have demonstrated potent cholinesterase-inhibiting properties[65–68]; with 1, 8 cineole alone evincing the greatest effects[65]. These CNS effects produce enhanced secondary memory, accuracy and attention in healthy aged (over 65 years) participants[69] and consumption of this terpene, in the form of an essential oil, is reportedly well tolerated in a small group (*n* 11) of patients aged 76–95 years with mild–moderate AD following 6 weeks of 50–150 µl daily consumption of *S. officinalis*[70]. The

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latter study did not observe any statistically significant cognitive benefit but this was not the *a priori* aim of the study and this is reflected in the sample size. Nevertheless the authors do report positive indications on the cognitive test battery used (Cognitive Drug Research) and this is in line with the only other trial investigating the benefit of sage in AD[71]. Here nineteen participants (65–80 years), with mild–moderate AD, consumed an *S. officinalis*-alcoholic tincture for 16 weeks and better outcomes on the ADAS-cog, compared with the placebo controls, was observed. This study also demonstrated a trend towards reduced agitation in the *S. officinalis* group.

Potential benefit of phenolic phytochemicals against Alzheimer's disease

Currently about 10 000 compounds have been classified as polyphenols and this large class comprises both flavonoid and non-flavonoid forms. The former comprise the largest grouping and these can be further sub-divided into isoflavones (found in soya and soya products), flavones (found, for example, in sweet pepper), flavanones (found in citrus fruits), flavanols (which can be further sub-categorised into flavan-3-ols (found in tea) and proanthocyanidins (found in fruits)), flavonols (fruits and vegetables; specifically onions) and anthocyanins (specifically found in berries)[72].

Epidemiological data have established links between the consumption of polyphenol-rich diets, and specific polyphenols, and reduced incidence of AD in human populations. Consumption of fruits and vegetables and total levels of flavonoids are associated with protection against, or slowed progression of, AD and other dementias[73–75]. Large cohort studies have also evidenced links between neurocognitive protection (as indexed in all cases by scores on the Mini Mental State Exam) and tea consumption in elderly cohorts[76,77] as well as chocolate and red wine[78].

Resveratrol

Resveratrol derives from a sub-class of non-flavonoid polyphenols termed stilbenes and is found in limited sources, which include grapes and, as a result, wine. Resveratrol has received much research attention regarding its potential to benefit a number of disease states, including CVD[79], cancer[80] and even life extension in a range of animal models[81]. The many and varied health effects attributed to resveratrol are likely underpinned by the multifarious biological targets that it interacts with. These include, but are not limited to, cyclooxygenase 1 and 2, the sirtuins and various kinases and DNA/RNA and lipoproteins. These specific interactions explain how resveratrol is able to exert anti-inflammatory effects, to interact directly with cell signalling and its links to cardiovascular health, respectively[82]. Interaction with these targets, and others such as up-regulation of cerebral blood flow [6,7], and the ability of resveratrol to attenuate amyloid-β-induced cell death *in vitro*[83], suggests that this polyphenol should be capable of beneficial therapeutic potential in AD. Indeed, results from animal models supports the function of resveratrol here with reduced markers of pathology, e.g. amyloid-β plaques[84], and behavioural deficits, e.g. improved learning and memory[85], in response to resveratrol exposure and consumption (25 mg/kg per d) of resveratrol, respectively.

However, to the best of current knowledge, only one study exists, which investigates resveratrol in human volunteers with AD. Here a phase-2 randomised, placebo-controlled, double-blind 12-month trial of 500 mg/d (escalating to 1000 mg twice daily) resveratrol was conducted in participants with mild–moderate AD[86]. Unfortunately the therapeutic measures of the present study were limited and, whilst amyloid-β markers were reduced by resveratrol, this was not more significant than in the placebo group, and brain volume loss was not attenuated. Resveratrol consumption was generally well tolerated, but participants did report significant gastrointestinal problems and weight loss, which is likely due to the high dose being received after escalation as these side effects are not seen often in the literature with doses at or lower than 500 mg.

Conclusions

This review began with the assertion that our current alkaloid phytochemical-derived AD pharmaceutical treatments, such as galantamine and rivastigmine, produce unpleasant side effects and, ultimately, target only one of the multifactorial deficits of this progressive neurocognitive disorder. Attenuating cholinergic decline is arguably the most important and easily influenced of the AD deficits, within our current capabilities, but this report argued that the terpene and phenolic groupings of plant phytochemicals might offer an equally efficacious and safer alternative for AD drugs, relative to the alkaloids, which also target multiple deficits.

The terpene and phenolic studies presented here are few and a clear, overall view is hindered by heterogeneous trials where sample size, method of assessment, trial length, route of administration and individual differences associated with pre-AD status and current severity of symptoms vary or are not considered. Another area which future studies should focus, and something which resonated from several talks at the Nutrition Society spring conference, is the concept of 'responders' and 'non-responders' in phytochemical research. These terms refer to individuals who experience an anticipated pharmacokinetic response to consumption of drugs, and those who do not, respectively; with this phenomenon based on a whole host of known and unknown factors. This likely includes the speed of gut transit, the microbiotic profile of the gastrointestinal tract and the functionality of efflux pumps, alongside multiple other variables, and these factors will be unique to each participant. It is likely that the impact of these individual differences will be diluted in large cohorts but, apart from the meta-analyses discussed, one common factor across terpene and phenolic research trials is relatively small

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sample sizes. Studies with these phytochemicals undoubtedly hold promise but robust and replicable outcomes will not be evinced until the above methodological constraints are addressed.

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Conflict of Interest

None.

Authorship

Dr E Wightman devised and investigated this research question and takes sole ownership of the written content.

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