Review Article
An exploration of the potential mechanisms and translational potential of five medicinal plants for applications in Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is the most common type of dementia, and represents a vast worldwide socio-economic burden, and in the absence of a current cure, effective therapeutic strategies are still needed. Cholinergic and cerebral blood flow deficits, excessive levels of oxidative stress, neuroinflammation and glutamate excitatory mechanisms are all believed to contribute to the development and progression of the disease. *Scoparia dulcis, Catharanthus roseus, Sesamum indicum, Erythrina senegalensis* and *Vigna unguiculata* represent five plants that have been used as traditional medicines for the treatment of AD in certain cultures. Review of the scientific literature was conducted to explore the properties of these plants that might be beneficial and explain what would be perceived by many to be largely anecdotal evidence of their benefit. All plants were found to possess varying levels of anti-oxidant capability. *Scoparia dulcis* was also found to potentiate nerve growth factor-like effects upon cell lines. *Catharanthus roseus* appears to inhibit acetylcholinesterase with relatively high potency, while *Sesamum indicum* demonstrated the strongest antioxidant ability. Comparisons with currently used plant derived therapeutics illustrate how these plants may be likely to have some therapeutic benefits in AD. The evidence presented also highlights how appropriate dietary supplementation with some of these plants in various cultural settings might have effects analogous or complementary to the so-called protective Mediterranean diet. However, prior to embarking on making any formal recommendations to this end, further rigorous evaluation is needed to better elucidate the breadth and potential toxicological aspects of medicinal properties harboured by these plants. This would be vital to ensuring a more informed and safe delivery of preparations of these plants if they were to be considered as a form of dietary supplementation and where appropriate, how these might interact with more formally established therapies in relation to AD.

Keywords: Alzheimer's disease, oxidative stress, hypertension, diabetes, neuroprotective, cholinergic, scoparia dulcis, catharanthus roseus, sesamum indicum, erythrina senegalensis, vigna unguiculata

Introduction

Dementia is defined as a group of disorders that have a pronounced and progressive deterioration of cognitive function that is so severe it affects a person's ability function independently in their day-to-day lives. Alzheimer's disease (AD) is the most common form of dementia characterised by an insidious onset of memory loss that relentlessly worsens, coupled with, and most likely caused by, neuropathological changes to the brain at both macroscopic and microscopic level. One of the initial symptoms of AD is a loss in the short term memory while progression of the disease is marked by a continuous decline in cognitive function, such as abstract thought, language and decision making processes. Moreover, depression, psychosis and aggression can occur in the latter stages of the disease.

The macroscopic changes observed in AD relate to significant atrophy in the brain that is underpinned by neuronal loss and consequent synaptic failure [1]. Visualisation of this by MRI is now becoming a key outcome measure of

progression in clinical trials for new therapies of AD [2]. This is helped in no small part by research by Fox and colleagues [3] and many others as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI), the latter being a large multicentre project aimed at identifying and validating biomarkers that will facilitate early diagnosis of dementia, whilst also allowing monitoring of disease progression and response to treatment [4]. Trials using protocols derived from ADNI findings show there to be a decreased efficacy with respect to commonly used anti-dementia treatments than previously thought [5]. Thus there remains a need for new treatment modalities – particularly those that may have disease-altering effects – and the plant kingdom represents a potential source for such candidates.

Microscopic examination of brain tissue from an AD patient highlights a number of key pathological hallmarks of the disease. These include intracellular neurofibrillary tangles (NFTs) made up of hyperphosphorylated microtubule-associated tau protein and numerous extracellular deposits known as senile plaques which are formed predominantly around a core of amyloid beta (Aβ) peptide [6]. Eventually these microscopic changes and the secondary mechanism they evoke contribute to a gradual decline in the function and number of neurons and synapses with an eventual progressive loss in brain mass, which underpins the diminishment in cognitive function. This pathology is also exacerbated by the deposition of Aβ in blood vessels, in the form of cerebral amyloid angiopathy, which is present in almost all cases of AD and which is a risk factor for intracerebral haemorrhage [7]. At the very advanced stage, people with AD are susceptible to various comorbidities which can result in their death [8], but which is sometimes recorded as the cause of death thereby potentially contributing to an underestimate of the mortality rates attributable to AD.

Epidemiology

In 2010 the worldwide prevalenceof dementiawas estimated at 35.6 million [9], with 5.4 million Americans living with AD [10]. Overall estimates suggest that there will be doubling of the number of people over 65 years by 2030 [11]. By the year 2050, the worldwide prevalence of AD has been estimated to increase by a factor of four to 106.2 million, which equates to one person in eighty five having the disease [10]. Given the continual improvements to life expectancy thanks to on-going advances in modern medicine, increased rates of dementia seem to be inevitable unless medical improvements also incorporate a way to fully halt or prevent AD. These projected increases also have a considerable emotional and financial burden with estimated costs to a person with AD over their entire life being as much as $175,000 [11].

Yet, there are reports of reduced incidence rates in the Mediterranean population [12]. It has been postulated that the Mediterranean diet, which is high in antioxidants, may have a protective role. However, other confounders such as thehigher prevalence of β thalassemia minor, reported to be up to 16% in Cyprus [13], which can result in decreased blood pressure and viscosity [13] could also be a contributing factor since high blood pressure is widely reported as a risk factor for dementia and AD [14]. Other sources of confounding to accurate estimation of incidence rates are reported gender differences in AD, with females having an increased risk, particularly amongst the most elderly [15] and yet women live longer certainly on average while the female sex hormone oestrogen may be protective against the development of AD [16]. Similarly advancing age, the most recognised risk factor for the development of dementia may also be a factor. Thus a complex interaction between higher life expectancy in women and oestrogen deficit in post menopausal women [17] are likely to contribute to gender differences observed in AD.

The pathogenesis of AD

In order to fully comprehend mechanisms by which new therapies might effectively combat AD, an understanding of the pathophysiology of the disease is required. In addition to the aforementioned hallmarks of the disease, there are a number of other important mechanisms involved in the pathogenesis of AD.

Aβ pathology

As mentioned, aclassical hallmark of AD is the deposition of Aβ-laden extracellular amyloid plaques and also its deposition in blood ves-

sels. Aβ arises from the cleavage of the much larger Aβ precursor protein (APP) [18]. Throughout life the majority of APP cleavage is carried out by α-secretase, producing sAPPα, a fundamental component of neuronal signalling. APP is also processed via the so-called amyloidogenic pathway, whereby it is cleaved sequentially by β- and γ-secretases to produce Aβ fragments, mainly of 40 and 42 amino acids in length and which are commonly known as Aβ40 and Aβ42 respectively [19]. In AD there appears to be an increase in Aβ fragments from the amyloidogenic pathway that is believed to be due to a subtle increase in the activity of this pathway, combined with interference to the normal systems involved in the clearance of Aβ from the brain [20]. These Aβ peptides can exist in many soluble and insoluble structural forms, importantly their aggregation into insoluble multimeric forms is a pretext to them forming senile plaques. Various species of these transitional forms of Aβ are thought to disrupt the normal functioning of neurons including long term potentiation which is involved in memory [21], disruption of mechanisms involved in the signalling of neurotransmitters such as acetylcholine (ACh) that ultimately contribute to the death of neurons [22].

Tau pathology

Neurofibrillary Tangles (NFTs) occur when the tau protein, critical to the functioning of microtubules, becomes hyperphosphorylated through GSK3β-dependent and other mechanisms [23, 24]. This is then thought to contribute to the separation of tau from the microtubular network, permitting the aggregation of tau into NFTs [25]. The formation of NFTs is thought to have a detrimental effect on many of the transport processes that exist within neurons to allow them to function properly and maintain themselves [26].

Together with Aβ, NFTs that are thought to be a secondary manifestation of Aβ-induced changes, function to perturb cellular homeostasis and thus increase the production in reactive oxygen species (ROS) that exacerbates the disease process [27]. This is supported by increased levels of protein [28] and lipid [29] oxidation products present in post-mortem brain tissue. Therefore, compounds containing antioxidant activity have therapeutic potential.

Risk factors for AD

Hypertension

Increases in systolic and diastolic blood pressures have been found to occur prior to the onset of dementia by approximately 15 years [30]. Moreover, an elevated systolic blood pressure was found to lead to the presence of plaques in the neocortex and hippocampus, with an elevation in the diastolic blood pressure being related to an increased prevalence of NFTs in the hippocampus [31]. To date there has been considerable success in the therapeutic management of a considerable proportion of people with hypertension by using various pharmacological compounds. The renin angiotensin system (RAS), one of the main mechanisms that regulates blood pressure through the action of angiotensin II (Ang II), also appears to have a more intimate relationship with AD since drugs that inhibit the formation of Ang II (ACE-inhibitors) or its signalling (angiotensin receptor antagonists – ARAs) through its receptor AT1R appear to have protective effects on the incidence of AD [32, 33] or its rate of decline [34-37]. Similarly other anti-hypertension drugs such as calcium channel blockers (CCBs) may have more AD-related facets [38], but of the blood pressure related mediators, Ang II appears to have many links with AD pathology [39]. However, importantly, formal clinical trials of anti-hypertensive drugs in AD have yet to be undertaken.

People with hypertension are also likely to be susceptible to vascular and cerebrovascular changes, with atherosclerosis common and brain ischaemia likely. Ischaemic stroke has an exacerbating influence on the buildup of Aβ [40], possibly through the induction of the expression of the presenilin genes that form part of the amyloidogenic pathway based γ-secretase complex responsible for the formation of Aβ from APP [41].

Diabetes mellitus

Diabetes mellitus is another risk factor in the development of AD [42]. The fundamental trait of diabetes that is very relevant to AD is hyperglycaemia, which has been shown to play a role in neuronal damage as well as exacerbating oxidative damage [43]. Elderly patients with diabetes had a threefold increased chance of scoring

lower in a mental state examination [44]. Furthermore, a prospective cohort study of non-demented patients with type 2 diabetes found that the risk of acquiring AD was approximately doubled [45]. It has even been hypothesised that AD is a type 3 diabetes, or diabetes of the brain, due to similarities in amyloid deposition, insulin processing and oxidative stresses [46]. Moreover, antidiabetic medications used in patients with dementia or mild cognitive impairment may be beneficial [47].

Aim of this paper

We present a non-systematic review of the current literature on the potential therapeutic properties of five medicinal plants, *Scoparia dulcis, Catharanthus roseus, Sesamum indicum, Erythrina senegalensis and Vigna unguiculata* that have been used traditionally and often ancestrally to treat ailments such as hyperglycaemia, hyperalgesia, the treatment of AD-like conditions, high blood pressure, and even the common cold, in regions of West Africa. In doing so it attempts to explore evidence to support why they may be continually used in the contexts known and whether they could inform the development of dietary supplementation strategies in other countries against increasing rates of cognitive decline and dementia.

Literature review methodology

A search of Medline and Embase yielded 202 papers which may be relevant. MESH terms combined with OR: "Antioxidants", "Reactive Oxygen Species", "Free Radical Scavengers", "Antihypertensive Agents", "Hypertension", "Blood Glucose", "Hypolipidaemic Agents", "Plant Extracts", "Humans", "Animals", "Alzheimers Disease", "Dementia". This search strategy was then combined with the names of each of the five plants in turn (*Scoparia dulcis, Catharanthus roseus, Sesamum indicum, Erythrina senegalensis* and *Vigna unguiculata*) using AND as a linking term.

As a means to provide some form of comparison and baseline against which these candidates could be considered, we also gave some consideration to some other so-called medicinal plants that have been proposed as beneficial for AD. These comparisons can therefore allow some manner with which to assess the potential of the reviewed plants, as a way of perhaps prioritising one or more for more in further depth and rigorous pre-clinical lines of investigation.

Medicinal plants previously proposed for Alzheimer's disease

Ginkgo biloba

As a member of the conifer family and native to China, *Ginkgo biloba* (*G. biloba*) has been used extensively in Chinese herbal medicine [48] and has also been tested in Westernised medicine for the treatment of seasonal depression [49] and AD [50-52]. Commonly available as a nutritional supplement in everyday stores, *G. biloba* represents one of the most widely available medicinal plants. Traditionally used for the treatment of circulatory problems, it was later suggested to have an effect upon cognitive function, including AD [50], with the standardised extract, EGb 761, showing similar efficacy to donepezil [52]. Leaf extracts are rich in flavonoids, which have pharmacological properties akin to various neurotransmitter inhibitors [51], and improved memory and cognitive function in rats [53]. EGb 761 displayed protective effects on APPsw PC12 cells, that are cells expressing a mutated variant of the human APP gene that ordinarily causes familial forms of AD and in these cells causes increased production of Aβ [54]. EGb 761 also reduced the effects of free radical insult, that ordinarily causes apoptosis, in a dose dependent manner [54].

G. biloba is thought to have positive effects against AD due to its antioxidant properties. One example dictates the dose dependent inhibition of free radical production by EGb 761 after the administration of Aβ to PC12 cells [55]. PC12 cells pre-incubated with EGb 761 before exposure to Aβ showed reduced levels of reactive oxygen species generation, however it appeared that the ameliorating effects were anti-oxidative and not anti-cytotoxic from the Aβ exposure [55]. Yet, EGb 761 appeared to inhibit the formation of small oligomers of Aβ [55], while other findings suggest the compound was capable of modifying the anti-Aβ processing of APP through upregulation of α-secretase [56]. However, it has also been noted that *G. biloba* also possesses some undesired effects, EGb 761 upregulates the expression of tau in vivo which may be relevant

with respect to how hyperphosphoryated tau gives rise to characteristic neurofibrillary tangles in AD [57]. Moreover, mixed results in respect of clinical trials have arisen (NCT00276510). Administration of 120 mg extract twice daily had no effect in preventing the progression to AD [58]. Similarly, systematic review of *G. biloba* in AD have suggested that it outperforms placebo with moderate effect sizes, however, the clinical relevance remained hard to determine [59].

Galantamine

The alkaloid galantamine has been shown to be the ingredient of members of the Amaryllis family that displayed therapeutic benefits against AD. Alkaloids are naturally occurring compounds containing a central nitrogen atom, and have been widely reported to have medicinal uses [60]. Galantamine was originally isolated from the *Galanthus* species, and in modern times it is extracted from a range of plants [61]. However, galantamine is an existing treatment for mild AD, its therapeutic effects due its reversible antagonism of acetylcholinesterase (AChE) that degrades the memory neurotransmitter acetylcholine (ACh) [62]. As such galantamine is used to counter the cholinergic deficits mechanisms of AD, which have been demonstrated in clinical trials ranging from 3 to 6 months where improvements in (or less decline) in cognitive function were demonstrated [62].

Galantamine crosses the blood brain barrier due to its hydrophobic nature, similar to the AChE inhibitor physostigmine, although is not as potent [63]. Galantamine also offers some neuroprotective features, it has been shown to reduce neurodegeneration caused by ROS induced by Aβ, as well as positively influence antioxidant enzymes in preclinical studies [64]. However, numerous adverse effects have also been reported, with gastrointestinal symptoms the most common [65]. Other side effects with respect to cardiac function have also been noted, for example syncope, cardiac arrhythmias, and in some cases delirium [66], in addition to eliciting a hypertensive response in rats [67].

Cannabis sativa

Perhaps a more controversial plant is *Cannabis sativa* (*C. sativa*) that has reported therapeutic properties, including for the treatment of glaucoma, various cancers as well as multiple sclerosis [68]. The active component of *C. sativa* is tetrahydrocannabinol (THC) that has been suggested to have a number of properties that might counter the pathogenesis of AD. Much like galantamine, THC inhibits AChE [69]. Furthermore, THC is also thought to prevent Aβ aggregation, more potently than propidium, a more commonly known antagonist of Aβ aggregation [69], thus potentially offering disease-altering properties in relation to AD.

Similar to *G. biloba*, THC reduced the release of Aβ induced free radicals [70], and also has been reported to have antioxidant abilities which were neuroprotective [71]. Additionally, a non-psychoactive compound present in *C. sativa*, cannabidiol dose dependently inhibited the Aβ induced hyperphosphorylation of tau [72]. Cannabidiol has also been implicated in lowering the incidence of diabetes in rats [73], which is of interest considering diabetes is a recognised modifiable risk factor for AD and as such may have therapeutic benefit in the treatment of AD. However, *C. sativa* may be less viable because of its reported association with psychological problems [74-76].

New potential candidate medicinal plants for AD

Having summarised the mechanisms through which some of the current treatments for AD provide therapeutic benefit, as well as mechanisms proposed for some plants thought to have medicinal properties and which have received some degree of scrutiny using western medicine research methods, the potential of the five potential candidates proposed in this manuscript can be discussed.

Scoparia dulcis

S. dulcis, otherwise known as sweet broom weed, is a member of the foxglove family and is leafy in appearance scattered with small, white flowers. Indigenous to the rainforests, it possesses a number of proposed therapeutic properties. Anecdotally used by South American tribes people through methods involving decoction or simply brewing as a tea, the plant has been used for generations to treat menstrual problems, infections and as an analgesic. Chemical analysis has shown the most active

medicinal compounds in *S. dulcis* to be flavonoids and terpenoids [77].

Neuroprotective effects: There are no direct data showing the effects of *S. dulcis* on neuroprotection but given that they are rich in flavonoids there is some indirect evidence as to its potential. Nerve Growth Factor (NGF) dose dependently induced neurite outgrowth in PC12D cells, a cell model of sympathetic neurons, by upto 71% after 48 hours of exposure. Spectroscopic analysis identified two new acetylated flavonoid glycosides which were able to potentiate the effects of NGF by up to 16% [78]. However, two previously known compounds were found to have no effect upon neurite outgrowth [79].

A dose of 100 µg inhibited acetylcholinesterase by upto 58%, although this was significantly lower than the standard, galantamine [80]. In addition a cytoprotective effect was noted with respect to erythrocyte lysis.

Antioxidant ability: Male Wistar rats were fed aqueous extractions of 200 mg/kg *S. dulcis* over a six-week period to assess the activity ofthe antioxidant defence enzymes, catalase, superoxide dismutase (SOD) and reduced glutathione in brain tissue [81]. Catalase activity was changed the most, showing a 28% increase compared to a 9% decrease in SOD. On average the activities of all three markers only improved by 8.2%, which was statistically significant, although over all the observed modest improvements noted indicated that *S. dulcis* may not possess a great antioxidant effect. Yet, there remain questions as to whether water extraction is unfavourable in elucidating salient compounds.

Analogous experiments were conducted on a streptozotocin (STZ) induced model of diabetes in rats with more marked effects. In this model *S. dulcis* treated animals showed a maximum percentage increase of 219% for catalase activity, with a more modest increase of 42% from SOD [81]. On average, activities of all enzymes rose by approximately 130%. This contrasted with the normal rats, and was due to the nature of diabetes. Hyperglycaemia can deplete antioxidant stores, allowing free radicals to exert their potent effects upon neural tissue. In particular, diabetics show decreases in reduced glutathione, with *S. dulcis* increasing levels by 71% [81]. Given the links with hyperglycaemia in AD, these results suggest that *S. dulcis* exerts its greatest effects when antioxidant stores are low, in particular in diabetic rats, and as such may be more effective in pre-existing AD than as a disease prevention measure.

Two markers of lipoperoxidation, thiobarbituic-acid reactive substances (TBARS) and hydroperoxides, were found to be greatly elevated in these STZ induced diabetic rats [81]. *S. dulcis* negated the physiological effects giving risk to these markers and reduced them to near normal values. In support of this, water extracts of *S. dulcis* also exert antioxidant effects in a dose dependent manner [82]. Indeed, comparisons against the antioxidant vitamin E were made and the concentration of *S. dulcis* needed to obtain a similar antioxidative activity was 100 times higher [82].

S. dulcis also appears to have hepatoprotective effects that seem to stem from its free radical scavenging ability. An extract of the plant that was tested in hepatotoxic mice, and elevated the levels of the antioxidants SOD and glutathione in a dose dependent manner [83]. Oral administration at a dose of 800 mg/kg resulted in a two fold increase in the levels of both SOD and glutathione reductase compared with control [83].

The IC_{50} concentration of *S. dulcis* (i.e. that needed to reduce free radicals by 50% from the free radical store, 2,2-diphenyl-1-picrylhydrazyl (DPPH)) had a reasonable free radical scavenging ability with an IC_{50} of 38.9 µg/ml, although it is more than 10 fold less potent than the corresponding IC_{50} of 2.5 µg/ml for vitamin C [83]. The mechanism of action has been postulated to be through the constituent terpenoids, including scoparic and scopadulcic acids [81]. Terpenoids (i.e. terpene containing compounds) are known for their direct free radical scavenging abilities [84] although some studies have suggested these have poor antioxidant activity [85].

It may be the case that variation in reported IC_{50} values relate to the preparation methods used. Generally lower IC_{50} values were identified in studies using methods of slow drying followed by petroleum ether, diethyl ether and methanol extraction. Conversely, for studies

producing higher IC_{50} values a method involving sun drying followed by extraction with 95% ethanol was used. These two methods may have given rise to differential yields or types of phytochemicals, highlighting the need to compare methods of extraction when investigating a potential therapeutic candidate. Indeed, recent data has supported this whereby sequential extraction of S. dulcis using hexane, chloroform and methanol show that the pooled extraction yielded the most polyphenols while the chloroform extract yielded the most flavonoids and these gave rise to variable levels of support for the antioxidant ability of S. dulcis [86].

Another possible contribution to the variability in IC_{50} values includes the use of different species of mice in experiments. This combined with data suggesting that the combination of the phytochemicals, terpenes and flavonoids, is what drives S. dulcis mediated effects [77, 87, 88] are important considerations as well as the relative doses that are explored [89].

Antidiabetic effects: In studies undertaken in diabetic rats, the blood glucose levels have also been subject to analysis where S. dulcis was found to have a free radical neutralising effect and significantly reduce blood glucose concentration after six weeks of administration [90]. A small hypoglycaemic effect (a reduction of 1.83% at day 0) was observed immediately after administration to diabetic rats that steadily rose to a maximum reduction of 67.8% after six weeks of application [90, 91]. A similar, albeit more modest, hypoglycaemic effect was also found in normal rats. A very small reduction (0.43%) was found immediately after administration that increased to a maximum reduction of 13.8% after six weeks of application. Thus S. dulcis may have the potential to attenuate hyperglycaemia and reduce the rate of diabetes or metabolic syndrome induced cognitive decline. These effects have been replicated, with a dose dependent decrease in fasting blood glucose arising via a mechanism proposed to be related to altered consumption of glucose by cells present in the periphery [92].

Antioncogenic effects: The metabolites 4-epi scopadulcic acid B, isodulcinol and dulcidiol have been isolated from S. dulcis and are reported to have anti-oncogenic effects, through the inhibition of nitric oxide (NO) [93].

NO that is known to relax smooth muscle cells in the endothelium has also been shown to potentiate the effects of cancer cells, by stimulating metastasis and invasion [94]. Whilst inhibition of NO would be beneficial in aiding the eradication of cancer, it would also result in the removal of a vasodilator and thus could contribute to elevated blood pressure. IC_{50} values for the inhibition of NO by 4-epi scopadulcic acid B, isodulcinol and dulcidiol at 150, 100, 50 µg/ml respectively [93] have been reported and suggest a low level of efficacy for NO inhibition, yet hypertensive effects were still observed.

Adverse effects: As is often the case with synthetic medicines, naturally occurring compounds are likely to be no more different. Mutagenic effects have been observed for the flavone cirsitakaoside which is a compound present in S. dulcis [95]. Flavonoids, and flavones, are generally associated with their protective, antioxidant abilities and ability to scavenge free radicals [96], much like terpenoids. However, cirsitakaoside have been linked with a dose dependent increased frequency of chromatin and chromosomal breaks in vitro [95]. Furthermore, cirsitakaoside was found to inhibit mitosis [95].

These undesirable effects could ultimately bring into question the validity of S. dulcis as a therapeutic candidate for AD. These effects, coupled with the fact that hypertension is a prominent risk factor for the development of AD is also potentially damning. Yet, this breadth of studies exemplifies the broader issue of the need to explore a number of the facets of any disease of interest when considering the eligibility of new therapeutic candidates. It will likely be the case that the final decision as to whether a compound has potential will be based on its resultant overall net effect and a consideration based on any issues of safety.

Catharanthus roseus

Catharanthus roseus (*C. roseus*), belonging to the family *Apocynaceae* is a small plant, shrub-like in nature with numerous pink and white flowers. Europeans have utilised the plant as a treatment for diabetes, extracts have aided eye infections in the Caribbean, and in Central America it was used to combat the symptoms of the common cold [97]. However details of the specific extraction methods or parts of the

plant used in applications like these are generally unknown. Furthermore, *C. roseus* has been used in the management of many cancers, including breast cancers, leukaemia and Hodgkin's lymphoma [98]. It is generally believed that the alkaloids derived from the plant are the key to their efficacy, with vincristine and vinblastine of particular importance. These arise mainly in the leaves of the plants [99], with vincristine marketed as the anticancer drug Oncovin®, and works by a means of tubulin depolymerisation [100], inhibiting microtubule assembly, thus suppressing mitosis. Although these two alkaloids have shown therapeutic potential, over 70 additional alkaloids have also been identified, with some perceived to have possible applications for the treatment of AD.

Antidiabetic effects: As with *S. dulcis, C. roseus* was found to have antidiabetic effects. *C. roseus* extracts were shown to lower blood glucose levels in a dose dependent manner in both diabetic and non-diabetic mice [101]. Furthermore, at most doses the extract has more pronounced effects upon non-diabetic than diabetic rats [101]. Similar effects were seen in STZ induced diabetic rats, whereby aqueous extracts of the leaves and twigs elicited a 20.2% decrease in blood glucose for diabetic versus non-diabetic rats [102]. However, a dichloromethane-methanol (DCCM) extract of the plant produced more significant effects, where a dose of 500 mg/kg reduced blood glucose concentration by 57.6% over a 15 day period, together with delayed peak blood glucose after administration of 10 g orally relative to control [102]. Indeed, the DCCM extract, when applied for a month prior to administration of STZ, prevented the induction of diabetes in all of the experimental rats [102]. Thus *C. roseus* has some anti-diabetic properties, in terms of both primary prevention and also as a form of treatment of elevated glucose levels that may be relevant to decline in cognitive function.

Antioxidant ability: Changes to markers of oxidative stress, for example reductions in glutathione levels correspond with increases in oxidative stress. In some experimental conditions *C. roseus* was found to have a modest positive impact (15%) on raising glutathione levels [102], highlighting that it may possess free radi-

cal scavenging ability but it does not appear to be as potent as some of the other plants discussed. Using extraction methods favouring the isolation of phenols, different parts of the plant have been tested, including the leaves, stems, seeds and petals, each demonstrating a different antioxidant capacity. The petals were found to be the most potent free radical scavengers, with an IC_{50} for DPPH of 197 µg/ml, relative to the stems which showed the weakest activity with an IC_{50} of 476 µg/ml [103]. Overall the effects still are of modest potency compared to other plants but highlights the importance of careful evaluation of the entirety of plants to assess which areas may have most yield and effect.

Cholinergic effects: Of particular interest to AD is that *C. roseus* was found to have properties as an AChE inhibitor, similar to that of galantamine and other currently licensed AD treatments. The anti-cholinesterase activity was shown for leaf extracts whereby a concentration of 422 µg/ml was sufficient to inhibit AChE [104]. A similar AChE IC_{50} value (441.8 µg/ml) was obtained from stem extract, whereas petal extracts were much less potent (2683.1 µg/ml) [104]. *C. Roseus* appeared to have a maximal inhibition of 85%, with this activity mainly attributed to the presence of phenolic compounds [104]. Subsequent analysis showed that the roots of the plant had 16.5 times more anticholinesterase activity than the leaves and over 100 times higher potency than the petals. Furthermore, the roots were able to attain complete inhibition of AChE, further emphasising their effectiveness [105]. This increased effect was found to be due the presence of serpentine that served as a contributory factor. The IC_{50} of serpentine alone shows approximately 100 times increased potency compared to the roots. Thus it is that other compounds present in the root extracts exert inhibitory actions upon the activity of serpentine. Furthermore, an in vitro comparison of the currently employed anticholinesterase, physostigmine, *C. roseus* showed an IC_{50} value that was tenfold lower [105], and physostigmine appears to be one of the more potent cholinesterases [63] which therefore bodes well for *C. roseus* being used in a similar capacity. The structure of serpentine appears to be key to its potency as serpentine possesses a quaternary nitrogen, therefore having a positive charge, that is able to then

form ionic bonds with the negatively charged binding region of AChE [105]. Indeed, ajmalicine, the precursor for serpentine [106] that is traditionally known for its hypotensive capabilities, did not inhibit AChE and was comparable to the control [105]. However, ajmalicine did display antagonism of a nicotinic cholinergic receptor (nAChr) that serpentine appears to have no effect on [105].

Hypotensive effects: As described, the precursor of serpentine, ajmalicine (Raubasine®) exerts hypotensive effects through the blockade of the α-1 adrenoreceptor [107]. Inhibition of adrenaline and noradrenaline release decreases blood pressure. In addition, ajmalicine appears to have additional antioxidant capacity when it interacts with the growth hormone gibberellic acid [108], while increased levels of SOD and catalase have also been reported in investigations where giberellic acid was also added [108], thereby providing a superior free radical scavenging capacity. Of translational interest is that ajmalicine has been associated with improvement of cognitive function in elderly patients following stroke [78]. It is not clear if this relates to improvement or restoration of blood flow after a stroke and a combination of almitrine and ajmalicine has been shown to increase oxygen bioavailability, increasing cerebral blood flow [78]. This in itself is still of interest however since reduction in cerebral blood flow, is a common, and often early event in the pathology of AD and other forms of dementia [39].

Adverse effects: There is currently limited data regarding potential adverse effects of *C. roseus* that may be relevant to AD. Thus far, the only potential, negative effects of serpentine are that its precursor, ajmalicine serves an antagonist to some acetylcholine receptors in a concentration dependent manner [105]. The significance of these effects balanced against other effects would need to be explored in greater detail.

Sesamum indicum

More commonly known as the Sesame plant, it is cultivated mainly in Africa and Asia [109] predominantly as a source of sesame seeds. It is also an economically important plant and is extensively cultivated and used in the Middle East, as well as sesame seed paste being a key ingredient in the popular Mediterranean dip hummus. Traditionally the oil from this plant has also been extracted and used in complementary therapies, especially Indian Ayurvedic (i.e. a form of alternative) medicine.

Antioxidant ability: The main constituents of sesame oil are sesamin and sesamolin. These two lignans have enhanced dose dependent antioxidant ability relative to other oils when studied on hypoxic PC12 cells [110]. Concentrations of 50μm obtained from purified sesame oil restored SOD activity in hypoxic PC12 cells to control levels. Sesamolin appeared to have a stronger effect. Similar results were achieved with respect to the activity of catalase [110], showing that *S. indicum* has the potential to attentuate hypoxia-induced neurodegeneration through amelioration of free radical scavenging enzymes.

Analysis of phytochemicals present in extracts of sesame cake were examined and compared against endogenous and exogenous antioxidants [111]. The phytochemical compounds display ample free radical scavenging ability, with sesamol and sesamol dimers showing the most potent effects. Sesamol reacts with free radicals at a faster rate than α-tocopherol, an artificial antioxidant, and over 100 times faster than butylated hydroxytoluene (BHT). This further reinforces the potential effects of *S. incidumin* negating the effects of ROS in AD. Moreover, sesamin and sesamolin also demonstrated free radical scavenging ability and at a rate comparable to BHT and in other experiments, were able to inhibit the production of NO in microglial cells, mirroring the effects of *S. dulcis* [112]. These properties are thought to derive from their structure, with lignans in general known to possess various properties including antiviral and antitumorigenic actions thought to be due to a common methylenedioxy group [113].

However, there have also been studies where sesamin and sesamolin have not been shown to have antioxidant properties. Indeed, it is the metabolic products sesamol, sesamol dimers and to some extent sesaminol, that exhibit the observed effects [114]. The conversion of sesamolin to sesamol, and in turn to sesaminol, can be enabled by heat [115]. Oil from unroasted seeds displayed high constitutive values of sesamin and sesaminol, but when roasted at

250°C for 25 minutes, a tenfold increase in the concentration of sesamol was observed. This was associated with a corresponding two hundred fold decrease in sesamolin and a 5.8% decrease in sesamin [115]. Thus sesamolin likely acts as the precursor for sesamol, with the acquisition of sesamol only available after high temperature roasting.

Sesamol, a phenolic compound, has been reported to have various therapeutic effects, including protection from gamma radiation in mice [116] which involved preservation of some enzymes such as catalase, as well decreasing lipid peroxidation, showing a potential neuroprotective effect. Sesamol may also have anti-oncogenic properties whereby apoptosis is induced further to arresting the cell cycle [117]. However, the IC_{50} value of sesamol shows a lower activity than vitamin C, and thus when compared to the values of the other medicinal plants described in this review, sesamol appears to be a stronger free radical scavenger. Even the coat of the sesame seed are implicated in the inhibition of TBARS, which are secondary oxidation products [118]. This effect was not due to the sesamin and sesamolin, emphasising that heating is required to allow the anti-oxidant lignans, including sesamol, to be elucidated. The inhibitory effect of sesamol in relation to TBARS has been shown to be a dose dependent inhibition whilst also positively reducing levels of lipid peroxidation [119].

It should be noted that S. indicum is also rich in another antioxidant, γ-tocopherol, a type of vitamin E common to plants. Unlike the main tocopherol, α-tocopherol, the gamma form is more effective as a free radical scavenger and is more efficiently utilised by the body [120]. A one-month study into the effect of a modified diet that included sesame oils showed significant increases in the levels of γ-tocopherol in healthy Swedish females [121]. Increased plasma levels of tocopherols have been associated with a 45% decrease in the development of AD, highlighting strong therapeutic potential. Furthermore, an almost 20% increase in γ-tocopherol levels occurred after just three days of consumption of sesame seeds; the increase of γ-tocopherol levels is thought to be due to the sesame-derived lignan-mediated inhibition of γ-tocopherol breakdown. However, clinical trial data from the Alzheimers Disease Cooperative Study is contradictory towards the therapeutic benefits of tocopherols in the combat of AD. The two year study showed no efficacy from tocopherols, with the placebo group scoring higher in cognitive function tests [122]. Another three year study found no significant difference between the time taken to develop AD between the placebo group and tocopherol group [123]. Hence, due to the mixed nature of results from the tocopherols in the treatment of AD, further work must be undertaken with particular reference to the gamma form.

Neuroprotective effects: As previously mentioned, sesaminol, the metabolic product of sesamolin, has antioxidant ability, but also with respect to AD displays neuroprotective features against Aβ. Sesamolin glycosides were able to counter, in a dose dependent manner, the cell death induced by Aβ in PC12 cells [124]. These observations are likely contributed to by the sesaminol glycosides decreasing Aβ induced free radical production and therefore reducing levels of associated cell death. Even reduced levels of cell viability of up to 50% following exposure of PC12 cells to Aβ oligomers were almost completely restored by 250 μg/ml sesaminol glycosides [124].

Antidiabetic effects: There is limited information of anti-diabetic effects of S. indicum, but sesamol has been shown to elicit dose dependent reductions in plasma glucose of diabetic rats. A dose of 8 mg/kg equated to a 71.5% decrease in glucose levels compared to untreated diabetic rats after ten weeks [119]. The same level of exposure in non-diabetic rats also resulted in an 18.5% decrease in the plasma glucose concentration.

Cholinergic effects: Sesamol treatment has been shown to reduce the duration of time taken by diabetic cognitive impaired mice to escape from a known maze [119]. Sesamol also appeared to improve memory function to equivalent levels seen in the control group. The effects appeared to derive from inhibitory effects upon the acetylcholinesterase activity and this was observed in a dose dependency manner [119]. However, sesamol alone in the control group appeared to elicit no additional cognitive enhancement, highlighting that sesamol only appears to exhibit a benefit under pathological conditions. Thus sesamol demonstrates many of the qualities needed in a potential treatment for AD.

Erthythrina senegalensis

Erthythrina senegalensis (E. senegalensis) is a member of the *Fabaceae* family, and is normally cultivated for ornamental purposes, having an attractive appearance with distinctive, vibrantly coloured flowers [125]. Certain African tribes have used a decoction of the bark of *E. senegalensis* in order to treat hepatic problems [126]. The plant has also been used in Mali, West Africa, in order to combat a multitude of disorders, the most common being the treatment of amenorrhoea. Different parts of the plant are used including the root, flower and bark, and are consumed after the formation of a powder or decoction [125]. However, in some cases, honey or the *Cola nitida* nut are added [125], and it has yet to be shown whether some of the effects observed are from *E. senegalensis,* or involve contributions from these additives. Similar preparation methods are also used for the treatment of malaria, hyperalgesia, jaundice and other gastrointestinal illnesses [125].

Antioxidant ability: Investigation of the free radical scavenging ability of bark from the stem of *E. senegalensis* yielded three compounds of particular importance. Ethanol-based extraction revealed the compounds to be the diprenylated isoflavonoids, osajin, 2,3-dihydro-2-hydroxyosajin along with 6,8-diprenylgenistein [127].

E. senegalensis exhibits moderate free radical scavenging ability. Describing its effects in terms of EC_{50} values, which in this instance is comparable to the IC_{50}, 2,3-dihydro-2-hydroxyosajin demonstrated the most potent antioxidant ability [126]. However, the activity was still almost threefold less than that normally attributed to vitamin C, indicating low levels of potency. Yet, compared to *S. dulcis* it is more potent.

In other investigations using different methods to assess levels of anti-oxidant power, 2,3-dihydro-2-hydroxyosajin was shown to have a 8,500 fold less antioxidant potency relative to vitamin C [128]. Furthermore, the concentration of osajin needed to elicit the same inhibitory response as vitamin C was 10,000 fold higher. Thus, overall if candidacy were to be place solely on antioxidative properties, *E. senegalensis* would appear to be coming up short.

Yet, osajin has been showing to exert beneficial antioxidative properties in ischaemic injuries [129]. However, osajin derived from the fruit of *Maclura pomifera* appeared to perform poorly in vitro [130]. It is unclear, although perhaps unlikely, whether the different source of osajin may have contributed to differences in its potency.

Adverse effects: Erysodine, an alkaloid present in *E. senegalensis* was reported to antagonise neuronal nAChRs [131] that may support a mechanism by which cholinergic deficits in AD may be exacerbated. Indeed, agonism of nAChRs has elicited good efficacy in the treatment of AD, and contributes to improved cognitive function [132].

Toxicological analysis of *E. senegalensis* extracts in male and female Wistar rats showed that acute administration was safe, although doses above 5 g/kg resulted in decreased movement, in addition to a reduction in aggressiveness and response to pain at doses in excess of 10 g/kg [133]. These effects reflect impairment of nervous system function but which may also explain why tribes people in some countries utilise this plant as a means of pain relief. However, the long term consequences of exposure are largely unknown. Data from exposure for up to 28 days in rats showed no significant toxicological changes to organs or haematology [133].

Vigna unguiculata

Vigna unguiculata (V. unguiculata), more commonly known as the cowpea, is a legume used extensively around the world, with the cowpeas, or "black eyed peas", used as a food source. Already cultivated on over 7 million hectares worldwide [134], It is possible to see both socio-economic benefits, and scope for access to it, if therapeutic benefits for AD were supported. Traditionally the plant has been used to combat hypertension, with the beans produced by the plant perceived to achieve this effect. One preparation method observed is to pressure cook the cowpeas, which is common in Indian and Mediterranean diets. Furthermore, the liquid produced during the cooking processes is often combined with various spices in a perceived method of combatting the common cold [135].

Antioxidant ability: A study of the plants using the vitamin C and the trolox equivalent antioxidant capacity (TEAC) method compared the levels in raw and germinated seeds. Vitamin C was absent in ungerminated seeds, but there was a significant twentyfold increase in levels following germination [136]. Yet, the TEAC values showed that antioxidative effects were present in both ungerminated and germinated seeds and the size of effect was related to the time given allowed in which to germinate. Allowing the seeds to germinate for up to four days allowed for a 58% increase in antioxidant capacity [136].

Different varieties of cowpea are produced, denoted by colour that varies from white to brown. Vitamin C levels ranged from 0.5 mg/100 g to 0.9 mg/100 g across the different varieties [136]. Although these levels may be considered to be low, it may be the case that the synergism of all the compounds present enables the plant to possess its antioxidant ability. Phytate, a natural antioxidant essential to the development of plants [137], is also present and its levels range from 2.0% to 2.9%. Four main varieties are cultivated – brown, dark brown, brown drum, and light. The brown drum variety of cowpea has both the highest levels of vitamin C and phytate, with the brown variety showing the highest concentration of total phenols at 1 mg/g, indicating that this variety may serve as a potential candidate for future testing. The levels of phenols have been shown to be an important in determination of antioxidative ability [136]. However, this has correlated with a poor free radical scavenging ability. The light and dark brown varieties have showed the greatest ability with values of 705 mg and 618 mg needed to quench 50% of the free radicals present in DPPH, respectively, and this can be compared with a twenty-fold more potent activity for the standard, butylated hydroxanisole (BHA) [135]. Similar findings were observed using the ferric reducing antioxidant power (FRAP) assay with raw cowpeas exhibiting the greatest antioxidant ability [135]. In addition, the β-carotene linoleic acid model system (β-CLAMS) assay also showed that raw, brown variety had significantly higher antioxidant ability than heated or soaked cowpeas, although BHA exhibited a far superior inhibition of β-carotene [135]. Coupled with the fact that a dose dependent inhibition of superoxide was observed, and that good levels of hydroxyl scavenging were observed [135], it may be in fact a summation of all the different antioxidant abilities presented that allow *V. unguiculata* to effectively combat oxidative damage.

The effects of drought stress in *V. unguiculata*, suggestive of its antioxidant capacity and using levels of glutathione reductase (involved in the regeneration of reduced glutathione) as a marked showed relatively robust protection [138]. Similar examination of the plants the defensive capabilities assessed through the measurement of antioxidant activity in the periphery of the plant also revealed moderate levels of vitamin C but also high levels of important free radical scavenging catalase and glutathione reductase activity in the periphery [139].

Hypotensive effects: Interesting antihypertensive effects have been suggested for *V. unguiculata* via methods involving Flavourzyme® protease hydrolysis [140]. Unrefined hydrosylated products yielded by this method caused small levels (IC$_{50}$ value of 2634.4 µg/ml) of inhibition of Angiotensin Converting Enzyme (ACE), a primary pharmacological target for the treatment of hypertension. However, subsequent ultrafiltration of the hydrosylated products showed a more enhanced effect, with the largest effect produced by lower molecular weight peptides. The largest effect was from the smallest peptide derivative with a weight of less than 1 kDa that produced an IC$_{50}$ of 0.04 µg/ml for the inhibition of ACE. The lowest levels of inhibition resulted from a peptide of over 10 kDa in weight with an IC$_{50}$ of 170.6 µg/ml reported [140]. The potent ACE inhibitory activity observed in the lowest molecular weight peptide is suggestive of a potential treatment for AD, since reduction of blood pressure is largely considered to be beneficial in reducing risk of AD. Indeed, the fact that the inhibition is of ACE, is also important however since some current pharmacological inhibitors of ACE have been reported to have varying levels of beneficial effect on rates of cognitive decline and risk of AD in various studies [32, 33, 36, 141, 142]. An alternative approach to explore the properties of *V. unguiculata* using different enzymatic hydrosylation, with pepsin pancreatin hydrosylate (PPH), showed an enhanced IC$_{50}$ prior to ultrafiltration of 1397.9 µg/ml [140]. Yet this is significantly more potent than the equivalent value pro-

Table 1. Summary of AD-related physiological mechanisms and biochemical systems that are attenuated by current candidate and more commonly known plants

Plant Name	Biochemical and physiological mechanisms relevant to Alzheimer's disease					Potential adverse effects
	Antioxidant	Antidiabetic	Antihypertensive	Neuroprotective	Cholinergic	
S. dulcis	+	+	N/R	+	N/R	Mutagenic? Hypertensive?
C. roseus	+	+	+	N/R	+	Cholinergic Interference?
S. indicum	+	+	N/R	+	+	N/R
E. senegalensis	+	N/R	N/R	N/R	X	Cholinergic Interference?
V. unguiculata	+	N/R	+	N/R	N/R	α-synuclein-like protein of unknown impact?
G. biloba	+	N/R	+	+	+	Tau disturbances?
Galantamine	+	N/R	N/R	+	+	Gastroinstestinal and cardiac disturbances?
C. sativa	+	+	N/R	+	+	Psychological problems?

Reported positive effects (i.e. potentially beneficial) that may improve AD-related deficits are indicated by +; the absence of any reported effects is indicated by X; while the lack of any current evidence or investigation in any of the categories listed is indicated by Not Reported (N/R). Potential adverse effects of the plants reported are also summarised. No attempt has been made to try to do any comparative rating of plants across the various categories because of the frequent lack of standardised approaches and the scope for over interpretation of findings that may also be subject to some degree of publication bias. The occurrence of similar properties by the plants listed illustrates the scope for potential use in AD but which first require more systematic head-to-head comparisons using standardised methodologies to prioritise the strongest candidates for further translation.

duced by unrefined products yielded by Flavourzyme®, which may be due to the production of different or more bioactive peptides when PPH was used.

Adverse effects: V. unguiculata contains a protein which is similar to α-synuclein that is the main pathological hallmark of Lewy Body dementia and which is also seen in AD [143]. The identification of the so-called K segment of a 35 kD protein, subsequently found to be a dehydrin, has many similarities to α-synuclein, including having α-helical structures and partial sequence homology, but the significance of this remains unclear [144]. Furthermore, dehydrin may be involved in the formation of Aβ-laden senile plaques that are a hallmark of AD.

Conclusions

It is not possible to directly compare and contrast the five candidate plants presented above because it would be subject to a number of biases (e.g. assessment would be based on considerable publication bias, reflecting variable levels of interest and knowledge about the candidates as well as non-uniformity of experimental conditions even on similar areas of experimentation). In short, the only way to rigorously compare the plants would be in a systematic manner, using identical experimental methods on plants prepared in a standardised manner and across a standardised number of areas of focus. From what information has been reviewed here, it is possible to see how various preparations of these plants may have been attributed as of potential therapeutic value to AD (summarised in **Table 1**). That a number of the candidates inhibit AChE activity is consistent with current licensed therapeutic approaches for AD, whilst the potential benefits afforded by plants that may counter oxidative stress, diabetic-like symptoms and hypertension echo with the reported involvement of these processes as either factors that increase risk or the progression of AD. Yet, one must be cautious when considering how these may be used in complementary approaches to AD. For some of the candidates they may also carry some unwanted adverse effects such as having oncogenic properties or they may have hypotensive properties that are not tolerable in

elderly people with lower levels of blood pressure which might give rise to varying degrees of syncope and thus increase the rate of falls. It may be the case that to benefit from these plants on some levels it may require taking them in amounts that actually introduce other, as yet unknown toxicological effects in humans, particularly if taken chronically. Therefore, while a number of the reviewed plants may have some potential in AD, especially since a number appear to exert benefits in more than one of the pathogenic mechanisms that are attributed to AD, yet there also needs to be a systematic approach to how these plants are prepared and studied for therapeutic benefits. This would also require careful toxicological profiling and also the use of reference therapeutic standards against which they might be compared. In this way more direct comparisons could be interpreted from research on these plants and help in the making of a more informed choice as to which plants might be worth progressing further as a possible means of supplementing existing therapeutic approaches, which itself is something that would also need to be evaluated carefully.

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