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Plants as Potential Sources for Drug Development against Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder that primarily affects the elderly population and is considered to be responsible for ca. 60% of all dementia in people aged 65 or older. Due to its debilitating nature, an enormous social and economic burden is placed on society. The significance of AD is further compounded as the number of identified cases is estimated to double or triple by 2050. Currently there is no cure for the disorder and much of the treatments available have been able to only delay the progression of the disease or provide symptomatic relief for a short period of time. Therefore there is a need for a different approach to the treatment of these diseases. Plants have been used since antiquity in the treatment of various diseases including cognitive disorders, such as AD. Therefore ethnopharmacological screening of plants may provide useful leads in the discovery of new drugs for AD therapy. This article reviews screening of the plants, belonging to 21 families, used in traditional systems of medicine (e.g. Chinese, Indian and European) for treatment of cognitive dysfunction. Electronic data bases were used for searching information related to the studies done on the plants in the last 20 years. Phytochemical substances such as alkaloids, biphenolic lignans, curcuminoids, caffeic acid derivatives, diterpenes, triterpenoid saponins, triterpene lactones, stilbenes and withanolides with pharmacological activities relevant to AD treatment are discussed in this review. Compounds of potential interest for further drug developmental studies have been highlighted.

Keywords: antioxidant, anti-inflammatory activity, Amyloid β peptide, cholinesterase inhibition, ethnopharmacology, iron chelation, lipid peroxidation, traditional medicine

Abbreviations: **AD**, Alzheimer's disease; **AChE**, acetylcholinesterase; **Aβ peptide**, Amyloid β peptide; **AM**, Ayurvedic medicine; **BuChE**, butyrylcholinesterase; **ChAT**, choline acetyltransferase; **COX**, cycloxygenase; **5-HT**, 5-hydroxytryptamine; **KUT**, Kami-utan-to; **NGF**, nerve growth factor; **NMDA**, *N*-methyl-D-asparatate; **ROS**, reactive oxygen species; **RNS**, reactive nitrogen species; **TNF-α**, Tumour Necrosis Factor-α; **TCM**, traditional Chinese medicine

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Invited Review

INTRODUCTION

A reduction in birth rates and increased life expectancy has resulted in a quantitative increase in the mean population age. There has also been an increase in the incidence of age-associated diseases, e.g. arthritis, cardiovascular disease, diabetes, neurodegeneration, etc. Perhaps the most debilitating of these conditions are those that affect the nervous system. While the aetiology and pathogenesis of many age-related conditions may be affected by lifestyle changes or can be managed through pharmacological intervention, neurodegenerative disorders are either poorly responsive to such approaches or their progression appears unabatable. Of the neurodegenerative disorders, Alzheimer's disease (AD) is considered to be responsible for ca. 60% of all dementia in people aged 65 or older (Francis *et al*. 1999). Due to its debilitating nature, an enormous social and economic burden is placed on society. The significance of AD is further compounded as the number of identified cases is estimated to double or triple by 2050 (Fillit 2000).

None of the pharmacological lines of intervention have so far been able to stop the progression of AD (Small and Mayeux 2005); thus, a need for an alternative approach was believed necessary to make progress with particular emphasis on plants. Plants have been used since antiquity in traditional medicinal systems for the treatment of memory dysfunction. Studies carried out on some species have resulted in the identification of compounds which are currently either in clinical use or templates for further drug discovery, e.g. galantamine, an alkaloid isolated from *Galanthus nivalis* L. (Amaryllidaceae). Galantamine was approved by the FDA in 2004 for use as an acetylcholinesterase inhibitor in the treatment of AD (Jones *et al*. 2006). It was the traditional use of *G. nivalis* L. in Bulgaria and Turkey for neurological conditions that lead to the development of this drug (Shu 1998).

The importance of plant-derived compounds in drug discovery is evident from a glance at the Prescription Drug Audit (Jones *et al*. 2006): 35 natural product related drugs originally discovered from vascular plants were among the 150 top selling drugs in 1993 (Jones *et al*. 2006). The majority of plant-related drugs were discovered from ten plant species, nine of which had been used traditionally for medicinal properties that were related to the current therapeutic indication (Jones *et al*. 2006). This shows a clear correlation between the ethnomedical uses of the plants and the current use of their derived drugs. The strategy used for discovery of new drugs based on the screening of plants having medicinal uses relevant to the treatment of a particular disease, is referred to as ethnopharmacological screening (Samuelsson 2004a). This appears to be a particularly rewarding approach because it has been reported that, of 122 drugs derived from medicinal plant which are in use world wide, 80% can be traced back to their ethnomedical uses (Jones *et al*. 2006).

There have been previous reviews on the plants demonstrating pharmacological and clinical effects of potential interest in AD therapy, including Clement *et al*. (2004), Howes and Houghton (2003), Howes *et al*. (2003), Kumar (2006) and Zhang (2004). By studying the reviews it becomes clear that ethnopharmacological screening is one of the main approaches used in drug discovery. Some of the preclinical and clinical studies related to AD, carried out with medicinal plants have been mentioned in **Table 1**. The following is a review of the plants and the phytochemical substances which have shown to be of therapeutic potential in AD therapy.

ALZHEIMER'S DISEASE AND MAJOR PHARMACOLOGICAL INTERVENTIONS

Alzheimer's disease is a progressive neurodegenerative disorder characterised by impairment in learning and memory followed by more global cognitive deficits and behavioural disturbances (i.e. depression, agitation and psychosis), which become progressively more severe. The pathology of AD is

Table 1 Examples of pharmacological and clinical studies on medicinal plants which are relevant in AD therapy.

Plant	Extract	Extraction	Material	Dosage	RA[a]	Model	Reference
Acorus calamus							
	50% EtOH[b]	N.S.[c]	Rhizome	25 mg/kg/day	*p.o*[d]	Animal	Shukla *et al*. 2002
Bacopa monniera							
	EtOH	N.S.	N.S.	N.S.	*p.o*	Animal	Vohora *et al*. 2000
	H_2O	Distillation	Plant	30 mg/kg/day	Post. op[e]	Animal	Russo and Borelli *et al*. 2005
	50% EtOH	N.S.	Stem/leaf	5/10 mg/kg/day	*p.o*	Animal	Bhattacharya *et al.* 2000
	EtOH	N.S.	N.S.	300 mg/day	*p.o*	Human	Stough *et al*. 2001
	EtOH	N.S.	Stem/leaf	5/10 mg/kg/day	*i.c.b.v*[f]	Animal	Bhattacharya *et al.* 1999
	N.S.	N.S.	Rhizome	300/400 mg/day	*p.o*	Human	Kumar 2006
Biota orientalis							
	EtOH	N.S.	Seed	250/500 mg/kg/day	*p.o*	Animal	Nishiyama *et al*. 1995a
	EtOH	N.S.	Seed	250/500 mg/kg/day	*p.o*	Animal	Nishiyama *et al*. 1995b
Celastrus paniculatus							
	Fixed oil	Pressed	Seeds	50/200/400 mg/kg/day	*p.o*	Animal	Gattu *et al.* 1997
	H_2O	Infusion	Plant	100/200/300 mg/kg/day	*p.o*	Animal	Kumar and Gupta 2002a
	Fixed oil	Reflux	Seed	3 g/kg *t.i.d*[g]	*p.o*	Animal	Nalini *et al*. 1995
Centella asiatica							
	50% EtOH	Percolation	N.S.	5 mg/kg/day	*p.o*	Animal	Sakina and Dandiya 1990
	H_2O	Infusion	Plant	100/200/300 mg/kg/day	*p.o*	Animal	Kumar and Gupta 2002b
C. ternate							
	H_2O	N.S.	Rhizome	100 mg/kg/day	*p.o*	Animal	Rai *et al*. 2002
	EtOH	N.S.	Aer.[h]/, rhizome	300/500 mg/kg/day	*p.o*	Animal	Taranalli and Cheeramkuzhy 2000
Coptis chinensis							
	50% EtOH	Maceration	Plant	0.5 mg/ear	Topical	Animal	Cuéllar *et al.* 2001
	MeOH[i]	Maceration	N.S.	0.5 g/kg/day	*p.o*	Animal	Hsieh *et al*. 2000
Crocus sativus							
	EtOH	N.S.	Pistil	125-250 mg/kg	*p.o*	Animal	Abe and Saito 2000
Curcuma longa							
	H_2O	Maceration	Rhizome	140/280/560 mg/kg/day	*p.o*	Animal	Yu *et al*. 2002
Evodia rutaecarpa							
	80% MeOH	Reflux/LLE[j]	N.S	100 mg/kg	*i.p.*[k]	Animal	Park *et al*. 1996
Ginkgo biloba							
	Aq.ROH[l]./	Reflux	Leaf	240 mg/day	*p.o*	Human	Maurer *et al*. 1997
	Aq. ACN[m]/						
	An.MeOH[n]						
	Aq.ROH./	Reflux	Leaf	50 mg/day	*p.o*	Animal	Löffler *et al*. 2001
	Aq. ACN/						
	An.MeOH						
	N.S	N.S	Leaf	50/100/120/240 mg	*p.o*	Human	Rigney *et al*. 1999
	Aq.ROH./	Reflux	Leaf	120 mg/day	*p.o*	Human	Le Bars *et al*. 1997
	Aq. ACN/						
	An.MeOH						
	Aq.ROH./	Reflux	Leaf	100 mg/kg/day	*p.o*	Animal	Schindowski *et al*. 2000
	Aq. ACN/						
	An.MeOH						
Hypericum perforatum							
	50% EtOH	N.S.	Aer.	100/200 mg/kg/day	*p.o*	Animal	Kumar *et al*. 2000, 2002c
	80% EtOH	N.S.	Aer.	4/8/12/25 mg/kg	*i.p*	Animal	Khalifa 2001
	Crude powder			350 mg/kg/day	*p.o*	Animal	Trofimiuk *et al*. 2005
	Crude powder			Eq.Hy.[o] 4.3/13µg/kg/day	*p.o*	Animal	Tyszkiewicz *et al*. 2002
Melissa officinalis							
	45% EtOH	Maceration	Leaf	60 drops/day	*p.o*	Human	Akhondzadeh *et al.* 2003a
	30% MeOH	N.S.	Leaf	300/600/900 mg/day	*p.o*	Human	Kennedy *et al*. 2002
Piper methysticum							
	N.S.	N.S.	Rhizome	300mg	*p.o*	Human	Thompson *et al.* 2004
Polygala tenuifolia							
	80% EtOH	Maceration	Rhizome	10 mg/kg	*i.p*	Animal	Park *et al.* 2002
Salvia lavandulaefolia							
	Essential oil	N.S.	N.S.	25/50 µl/visit	*p.o*	Human	Tildesley *et al*. 2005
Salvia miltiorrhiza							
	MeOH	Maceration	N.S.	0.5/1 g/kg /day	*p.o*	Animal	Hsieh *et al*. 2000
Salvia officinalis							
	$CHCl_3$[p], EtOAc[q]	Soxhlet	Leaf	50-1000 µg/cm_2	*Topical*	Animal	Baricevic *et al*. 2001
	45% EtOH	Maceration	Leaf	60 drops/day	*p.o*	Human	Akhondzadeh *et al*. 2003b
Withania somnifera							
	N.S.	N.S.	Rhizome	50-200 mg/kg	*p.o*	Animal	Dhuley *et al*. 2001
	N.S.	N.S.	Rhizome	50-100 mg/kg/day	*p.o*	Animal	Naidu *et al*. 2006
	80% EtOH	Maceration	Rhizome, leaf	100 mg/kg/day	*p.o*	Animal	Dhuley *et al*. 1997
	Aq. EtOH	N.S.	Rhizome	20 mg/kg/day	*p.o*	Animal	Jain *et al*. 2001
	Rhizome powder			1000 mg/kg/day	*p.o*	Animal	Rasool and Varalaskhmi 2007

Abbreviations: [a]RA, route of administration; [b]EtOH, ethanol; [c]N.S., non specified; [d]*p.o*, *per os*; [e]*Post.op*, *post operatively*; [f]*i.c.b.v*, introcerebroventricular; [g]*t.i.d.*, ter in die; [h]Aer., aerial parts; [i]MeOH, methanol; [j]LLE, liquid-liquid extraction; [k]i.p, intraperitonial; [l]Aq. ROH, aqueous alkanol; [m]Aq. ACN: aqueous acetone; [n]An. MeOH, anhydrous methanol; [o]Eq. Hy, equivalent hypericin; [p]CH_3Cl_3, chloroform; [q]EtOAc, ethylacetate

a complex and a multifaceted one with several pathogenic pathways are believed to contribute to the progression of the disease, viz., senile plaque deposition, neurofibrillary tangle formation, inflammatory cascade, oxidative stress and cholinergic deficit (Small and Mayeux 2005). Based on these pathological hallmarks, several lines of pharmacological treatments have been investigated which are discussed.

Senile plaque deposition and anti-amyloid agents

A major component of senile plaques is the Amyloid β (Aβ) peptide which is formed as a result of proteolytic cleavage of the amyloid precursor protein (APP) by the secretases. According to the 'β-amyloid theory', it has been proposed that Aβ peptide deposits or even the partially aggregated soluble form are responsible for triggering a neurotoxic cascade of events which ultimately results in neurodegeneration (Castro *et al*. 2002). Therefore, modulating the chain of events starting from the production of Aβ peptide fragments from APP to its deposition in the form of extracellular plaques or even clearance of the already formed plaques are believed to be possible approaches toward the treatment of AD.

α-Secretase activity enhancers

α-Secretase is a membrane bound enzyme that hydrolyses APP within the Aβ domain thereby there is no Aβ peptide formed as a result of proteolysis. This is the major pathway of APP processing and is referred to as the non-amyloidogenic pathway (Blennow 2006). Promoting this pathway by enhancing the activity of α-secretase can be considered as a line of therapy; however, the problem is information about α-secretase enzyme is limited.

β- and γ-Secretase inhibitors

Another proteolytic pathway of APP processing is the amyloidogenic route. This involves cleavage of the APP at the extracellular and transmembrane domains by β- and γ-secratases, respectively. The result of the two proteolytic steps is the formation of Aβ(1-40) and Aβ(1-42) fragments with the former being the most abundant of the two species (Scorer 2001). The Aβ(1-42) fragment is the pathogenic species which aggregates more readily and forms amlyoid fibrils (Scorer 2001) Attempts at inhibition of these enzymes have been made, but the compound under investigation are in the early stages of testing and it will take several years before they reach clinical trials.

Aβ immunisation

One strategy used for targeting the Aβ peptide is the immunotherapy. The approach is based on immunisation of the subject against the peptide with the result that plaque deposition and the subsequent related hallmarks related to it are prevented. The problem with this approach, however, is that despite no adverse effects were reported in initial patient safety tests, during phase II trials signs of inflammation development in the CNS were observed.

Neurofibrillary tangle formation and tau inhibitors

One of the pathological hallmarks of AD is the formation of intracellular neurofibrillary tangles which consists of hyperphosphorylated tau protein. Tau is an axonal protein which binds to microtubules and by doing so promotes their assembly and stability. Phosphorylation of tau protein is regulated by the balance between multiple kinases (e.g. GSK-3β and CDK5) and phosphatases (e.g. PP-1 and PP-2A) (Blennow 2006). Hyperphosphorylation of tau protein starts in AD intracellularly and leads to sesquestration of the protein and other microtubule associated proteins, thus preventing microtubule assembly and impairing axonal transport. This results in neuronal function being compromised which ultimately precipitates neuronal death (Blennow 2006). Based on this pathogenic cascade, two principal lines of investigation have been proposed: (i) prevention of tau hyperphosphorylation and (ii) prevention of tau aggregation.

Preventing tau hyperphosphorylation

This approach address the imbalance in the kinase and phosphatase activities by inhibiting the action of protein kinases involved in phosphorylation of tau protein. There are several kinases implicated in tau phosphorylation such as glycogen synthetase kinase-3β (GSK-3β) and cyclin-dependent kinase 5 (CDK5) (Blennow 2006) which can be potential drug targets. The search for protein kinase inhibitors is an active one, however, to date, no kinase inhibitors have been launched as drug products (Castro *et al*. 2002).

Among the compounds which have demonstrated GSK-3β inhibitory activity, lithium, bisindolylmaleimides I (**1**) and IX (**2**) and thiadiazolidinones derivatives can be mentioned. Hymenialdisine, indirubin and paullones and even bisindolylmaleimides I and IV have shown CDK5 inhibitory activity (Castro *et al*. 2002).

One interesting development is that M1 muscarinic agonists AF102B (**3**), AF150(S) (**4**) and AF267B (**5**) are reported to have GSK-3β inhibitory activity (Fisher 2000). This unique feature of having the ability to alter different aspects of AD pathophisology is of considerable importance and further research on the nature of activity of these compounds is recommended.

Preventing tau aggregation

It is important to develop compounds that could be used to facilitate the proteolytic degradation of tau aggregates and prevent propagation of neurofibrillary tangles. Research has shown that selective inhibitors of cathepsin D are capable of preventing the formation for hyperphosphorylated tau fragments in a dose dependent fashion. Cathepsin D is a protease which is capable of cleaving tau protein at neutral pH and could be useful in regulating the formation of the precursors to neurofibrillary tangles (Bi *et al*. 2000). There is also selective inhibition of tau aggregation by diaminophenotiazines reported (Wischik *et al*. 1996). However there is more need for pharmacokinetic and toxicological studies.

Oxidative stress and antioxidant activity

The vulnerability of CNS to oxidative damage is due to a number of factors such as excessive oxygen uptake and high unsaturated lipid content. Under normal physiological conditions, damage by reactive oxygen species (ROS) is kept in check by antioxidant defence cascade consisting of enzymatic and non-enzymatic components (Valko *et al*. 2007). However, during degenerative processes there is an imbalance between ROS and cellular antioxidant defences, which leads to critical failure of biological functions. One of the sources of oxidative stress in AD is the disturbance in metal homeostasis such as iron, copper, zinc and aluminium, metals capable of catalyzing reactions that produce free radicals (Sayre *et al*. 2001).

Mitochondrial dysfunction, as source of ROS generation, has been proposed to be associated with variety of degenerative pathways leading to AD progression (Law *et al*. 2001). Aβ peptides are another important source of oxidative damage, producing neurotoxic effects directly by inducing more ROS and indirectly by activating microglia (Varadarajan *et al*. 2000). It has been proposed that Aβ peptides in the presence of transition metal ions produces ROS such as superoxide anion radical and hydrogen peroxide which are known to be responsible for oxidative damage *in vivo* (Varadarajan *et al*. 2000). Microglial activetion leads to a massive production of inflammatory cytokines, ROS and reactive nitrogen species (RNS), thereby contributing to oxidative damage (Scorer 2001). Therefore, oxidative stress and the inflammatory cascade working in

concert with each other have been proposed to play a significant role in the pathogenesis of AD.

Taking into account the various sources of oxidative stress, previously discussed, several pharmacological opportunities for influencing the disease can be suggested. One class of chemicals are those scavenging free radicals before they can bring about their deleterious effects. These include chemicals such as vitamins E (**6**) and C (**7**), selegiline (Phenylisopropylamines) (**8**), melatonin (indoleathylamine neurohormone) (**9**) and idebenone (a coenzyme Q analogue) (**10**), which have been used for different therapeutic purposes and have produced clinically significant results in AD studies (Castro *et al*. 2002). Neuroprotective effects of non-estradiol anti-inflammatory drugs by direct scavenging of nitric oxide radicals has opened up another avenue for treatment of the disease. Another group of antioxidants being investigated for the therapeutic potential are metal chelators (Castro *et al*. 2002). There are two aspects of their activity which are important: (i) by chelating the transition metal ions present in brain tissues, they inhibit their catalytic activity thereby preventing associated free radical generation which is termed as secondary antioxidant effect (Gordon *et al*. 1990) and (ii) by chelating the metals they prevent their subsequent binding to Aβ which prevents senile plaque deposition (Doraiswamy 2002). In a study carried out by Cherny *et al*. (1999), a copper/zinc chelator was capable of dissolving Aβ plaques. It has been shown that a mild to moderate chelating activity, which prevents metal ion binding to Aβ peptide, is preferred to strong chelating activity (Bush 2003; Ji and Zhang 2005). The former is referred to in the literature as the metal attenuation. A very good example is clioquinol (**11**) which showed desirable therapeutic efficacy in the initial stages of clinical trials (Doraiswamy 2002; Rosenberg 2003). AGE-inhibitors such as Tenilsetam (**12**) (are capable of inhibiting protein binding with sugars and the resultant sugar-derived oxidation (Durany *et al*. 1999). Another line of investigation is the inhibition of membrane lipid peroxidation, Lazabemide (**13**) being an example of such an inhibitor. Thus compounds can inhibit propagation of free radicals by partitioning into the hydrophobic membrane domain (Mason *et al*. 2000).

So far no antioxidant compound has been approved for clinical use, but clinical studies of these compounds continue in the hope of finding a suitable treatment in the near future. Some plants and their constituents which possess potent antioxidant activity have shown effects upon the CNS that are of relevance in the treatment of AD.

Inflammatory cascade and anti-inflammatory activity

Hallmarks of inflammation such as activated microglial cells and pro-inflammatory cytokines have been found in the post mortem brains of the AD patients. Clinical studies have also pointed out an increase in the level of inflammatory markers (Doraiswamy *et al*. 1997). Treatment of culture systems with fibrillier Aβ has lead to microglial activation and the subsequent production of inflammatory cytokines. This in turn results in the production of ROS and RNS (Scorer 2001).

Hence, anti-inflammatory agents have been used to attenuate microglia associated cytokine and free radical formation (Patricó and Trojanowski 2000). In this context, non-steroidal anti-inflammatory drugs (NSAIDs) have exerted demonstrable beneficial effects in relation to AD therapy (Castro *et al*. 2002). Several epidemiological studies pointed to an association between the use of NSAIDs and reduced risk of developing AD (Rich *et al*. 1995; Doraiswamy *et al*. 1997; Veld *et al*. 2001). Some of these studies have suggested that they may affect the age and onset of the disease. Many mechanisms have been proposed for their activity ranging from COX inhibition (Patricó and Trojanowski 2000) to lowering of amyloidogenic Aβ-42 peptide (Scorer 2001). Unfortunately, recent studies with NSAIDs such as celecoxib (**14**) and rofecoxib (**15**) were not beneficial in the treatment (Scorer 2001; Doraiswamy 2002). This shows that, it is unclear which anti-inflammatory targets are more relevant in the treatment of AD. Attention should be focused on clarification. Once resolved, there is a need for identification of novel molecular moieties with fewer adverse effects than the currently available drugs which are more effective in stopping the progression of the disease. Natural products can be a potential source for such novel moieties. For example numerous plant constituents have demonstrated anti-inflammatory properties (Handa *et al*. 1992; Bingöl and Şener 1995).

Cholinergic deficit and neurotransmitter replacement therapy

The selective degeneration of cholinergic neurons that originate in the basal forebrain and projects to the cortex and hippocampus results in the loss of all known cholinergic markers, such as choline acetyltransferase (ChAT), acetylcholine (ACh) levels and acetylcholinesterase (AChE). ACh is associated with cognition and it is the deficit of this neurotransmitter which contributes to cognitive dysfunction. The degeneration of these cholinergic neurons has been proposed to be a result of amyloid fibril-induced neuronal injury, tangle formation, ROS/RNS or astrocyte phagocytic activity (Small and Mayeux 2005).

On the other hand, ACh is known to promote non-amyloidogenic processing and reduce tau phosphorylation by reducing the activity of protein kinase which phosphorylates tau. Therefore, disruption of cholinergic signalling may lead to a feedback loop that increases production Aβ through altered APP processing, increasing phosphorylation of tau protein, thereby contributing to the progression of AD pathology (Lahiri *et al*. 2003).

Based on what has been mentioned above, restoration of the central cholinergic function may significantly improve cognitive impairment and may inhibit AD progression in patients. There are 3 principal approaches by which the cholinergic deficit can be addressed: (i) nicotinic receptor stimulation, (ii) muscarinic receptor stimulation and (iii) cholinesterase inhibition.

Nicotinic receptor stimulation

It has been reported that smoking may have protective effect against AD and nicotine (**16**) administration improved cognitive functions in AD patients as well as healthy elderly people (Newhouse and Kelton 2000; Min *et al*. 2001). It is also reported that nicotine increased the ACh level *in vivo* (Whitehouse and Kalaria 1995; Balfour and Fagerström 1996), thereby enhancing cholinergic neurotransmission in AD patients.

However, nicotine is not the only compound and therefore nicotinic receptor agonists have been used for the restoration of ACh levels (Houghton and Howes 2005). In a study carried out by Potter *et al*. (1999) ABT-418 (**17**), a novel nicotinic agonist, significantly improved declining cognitive functions in AD patients indicating that stimulation of central nicotinic receptors has an acute cognitive benefit (Kihara and Shimohama 2004). Currently, there is no nicotinic receptor agonist available for the treatment of AD patients, however there is research going in this field.

Muscarinic receptor stimulation

The rationale behind using compounds for their muscarinic agonistic action is to compensate for the low levels of ACh associated with AD. In addition to addressing the cholinergic deficits these agents also inhibit the fibrillary tangle formatin and Aβ production (Houghton and Howes 2005).

Currently there is no chlorogenic substance with muscarinic stimulation which has been marketed. However, research is going on in this field and some of the muscarinic compounds have shown promising results in animal experiments. Arecoline (**18**) and pilocarpine (**19**) are examples of

muscarinic agonist which have been tested for their cognitive enhancing function. Both the chemical are plant-derived alkaloids. They have provided template for further drug development research (Houghton and Howes 2005).

Cholinesterase inhibitors

Two types of cholinesterases, AChE and BuChE, are present in a wide variety of tissues. AChE, which is the predominant cholinesterase in the brain, hydrolyzes ACh to choline and acetate, thereby terminating the effect of this neurotransmitter at cholinergic synapses (Small and Mayeux 2005). AChE is, therefore, the target of cholinesterase inhibitors which are used for addressing the cholinergic deficit in AD patients.

Over the last two decades, cholinesterase inhibition has become the most widely studied and effective clinical approach to treat the symptoms of AD. Four cholinesterase inhibitors, tacrine (**20**), donepezil (**21**), rivastigmine (**22**) and galantamine (**23**) and have been approved by the United States Food and Drug Administration (FDA) for treating symptoms of AD. All these drugs are centrally active and were shown to improve memory and cognition in some patients with mild to moderate AD. However, this approach is limited, in principle, to patients who have intact and functionally active presynaptic neurons that are capable of synthesizing and releasing ACh. Therefore, AChEIs so far are only useful in the early stages of AD and lose effectiveness over time.

Increasingly, research has indicated the possibility that cholinesterase inhibitors in addition to providing symptomatic relief are having modulatory effects upon plaque deposition. Several recent studies using cell culture and animal models have shed light upon the effects of cholinesterase inhibitors at the level of Aβ peptide. Specific cholinesterase inhibitors exert amyloid lowering effect as a consequence of both their cholinergic and non-cholinergic activities: (i) cholinesterase inhibition results in an increase in ACh which as mentioned before will promote non-amyloidogenic processing (Lahiri *et al*. 2003) (ii) APP expression is suppressed with the result that the quantity of its proteolytic product, Aβ peptide, will also decrease (Shaw *et al*. 2001)

Butyryl cholinesterase inhibitory agents may be especially critical in light of co-localization of BuChE and amyloid plaques, Aβpeptide, NFTs and dystrophic neurons, all pathological hallmarks associated with AD pathology (Castro *et al*. 2002; Lahiri *et al*. 2003).

PLANTS AND PHYTOCHEMICALS OF POTENTIAL INTEREST IN ALZHEIMER'S DISEASE THERAPY

Medicinal plants

Acorus calamus L. (Araceae)

The plant *A. calamus* commonly know as sweet flag, is a perennial herb which grows mainly in swamps, marshes and river banks. In Ayurvedic medicine (AM), the rhizome has been used for the treatment of memory loss (Manyam 1999). Two rhizome extracts, ethanolic and hydroethanolic, exerted sedative and neuroprotective effects *in vivo* respectively (Vohora *et al*. 1990; Shukla *et al*. 2002) (**Table 1**).

Angelica archangelica L. (Umbelliferae)

A. archangelica is a perennial herbaceous plant used in traditional Chinese medicine (TCM) for treatment of cerebral diseases (Yang *et al*. 2005). An ethanol extract of the dried plant roots was capable of displacing nicotine from nicotine binding receptors in a concentration-dependent manner (Perry *et al*. 1996). Park *et al*. (1996) showed that a dichloromethane subfraction of a methanol extract inhibited AChE activity *in vitro*.

Bacopa monniera Wettst. (Scrophulariaceae)

B. monniera (**Plate 1A**), commonly known as water hyssop, is an annual plant found throughout the Indian subcontinent in wet, damp and marshy areas. In AM, the plant is used to improve memory and intellect. In India, this plant is locally known referred to as Brahmi or Jalanimab (Chopra *et al*. 1956). Ethanol extracts of aerial parts and rhizome from the plant possessed nootropic activity (Stough *et al*. 2001; Russo and Borrelli 2005; Kumar 2006) (**Table 1**). It has been suggested that this may be due to the bacosides being able to induce membrane dephosphorylation with a concomitant increase in protein and RNA turnover in specific brain areas (Singh *et al*. 1988). Alternative propositions include: (i) enhancement of protein kinase activity in the hippocampus (Singh and Dhawan 1997) and (ii) cognitive enhancement via its modulatory effect on the cholinergic system (Stough *et al*. 2001) (**Table 1**).

Bhattacharya *et al*. (2001a) (**Table 1**) showed that a standardised bacoside-rich extract from the leaf and stem of *B. monniera* reversed cognitive deficits induced by colchicine and ibotenic acid. In the same study the extract reversed the depletion of ACh, the reduction in ChAT activity and decreased muscarinic receptor binding in the frontal cortex and hippocampus. A similar extract of the plant demonstrated antioxidant activity in the rat frontal cortex, striatum and hippocampus (Bhattacharya *et al*. 2000) (**Table 1**).

A methanol extract of the plant inhibited NO-induced toxicity and prevented hydrogen peroxide-induced DNA cleavage *in vitro* (Russo *et al*. 2003a, 2003b).

Biota orientalis L. (Coniferae) Cupressaceae

The plant *B. orientalis* (**Plate 1B**) is an evergreen tree that grows mainly in South East Asia. The seeds of the plant have been used in TCM to relieve mental strain and to treat insomnia and amnesia (Nishiyama *et al*. 1995a; Lin *et al*. 2003). In a study carried out by Nishiyama *et al*. (1995b) (**Table 1**), S-113m (a herbal preparation composed of *B. orientalis*, *Panax ginseng* and *Schizendra chinesis*) preferentially improved memory registration and consolidation in mice. An ethanol extract of *B. orientalis* seeds improved memory dysfunction induced by amygdala and basal forebrain lesions in mice (Nishiyama *et al*. 1992, 1995a) (**Table 1**).

Celastrus paniculatus Willd. (Celastraceae)

The plant *C. paniculatus*, commonly know as black-oil tree is a large woody climbing shrub. In India it is known as Malkangni and has been mentioned in ancient Indian literature as an intelligence promoter (Nalini *et al*. 1995; Gattu *et al*. 1997) (**Table 1**). The seeds and seed oil have been used in AM as a memory enhancer (Nadkarni 1976). Nalini *et al*. (1995) reported that the seed oil reduced the levels of noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) *in vivo* (**Table 1**). In another study, the seed oil reversed scopolamine-induced task deficit (Gattu *et al*. 1997) (**Table 1**). Nalini *et al*. (1986) reported that treatment of mentally retarded children with the oil produced an improvement in their IQ scores.

An aqueous seed extract showed antioxidant effect in rat brain, which may be contribute to cognitive enhancing activity observed *in vivo* (Kumar and Gupta 2002a) (**Table 1**).

Ahmad *et al*. (1994) reported that a methanol extract of the inflorescences showed anti-inflammatory effect which may be relevant to AD therapy. A methanol extract was assessed for *N*-methyl-D-aspartate (NMDA) and γ-aminobutyric acid (GABA) binding activities and nerve growth factor (NGF) effects but did not show any response (Dev 1997). A possible explanation may be that the extraction solvent was polar and the seed oil and hydrophobic constituent may be responsible for the cognitive enhancing effects of *C. paniculatus*.

Plate 1 Aerial parts of (**A**) *Bacopa monnieri* Wettst; (**B**) *Biota orientalis* L.; (**C**) *Centella asiatica* L.; (**D**) *Clitoria ternatea* L.; (**E**) *Codonopsis pilosula* Franch. and (**F**) *Evodia rutaecarpa* var. *rutaecarpa* Benth.

Centella asiatica L. (Umbelliferae)

C. asiatic (**Plate 1C**) is a slender perennial creeper which grows throughout the tropical regions in the world. The leaf, known locally as Gotu Kola, has been used in AM for revitalising and strengthening nervous function and memory. For example, an Ayurvedic formulation composed of 4 herbs, including *C. asiatica* is used as a restorative and for the prevention of dementia (Manyam 1999). In TCM, it is also used to combat physical and mental exhaustion (Duke and Ayensu 1985; Brinkhaus *et al*. 2000).

An alcoholic extract of the plant possessed tranquilising and potentially cholinomimetic activities *in vivo*, which may be due to the presence of the triterpenoid brahminoside (Sakina and Dandiya 1990) (**Table 1**).

Aqueous extract of the whole plant enhanced cognitive function in rats, which was associated with the *in vivo* antioxidant activity of the extract (Kumar and Gupta 2002b) (**Table 1**). An aqueous leaf extract modulated dopaminergic, serotonic and adrenergic systems *in vivo* and improved learning and memory (Nalini *et al*. 1992).

The essential oil from the plant is reported to contain monoterpenes e.g. β-pinene and γ-terpinene (Brinkhaus *et al*. 2000), which have demonstrated AchE inhibitory activity, though not as potent as the standard reference substance (Perry *et al*. 2000).

Clitoria ternatea L. (Leguminosae)

C. ternatea (**Plate 1D**), commonly known as butterfly-pea, is a persistence herbacous perennial legume. The rhizome has been used in AM as a brain tonic and is reputed to pro-

mote memory and intellect (Misra 1998). In a study carried out by Taranalli and Cheeramkuzhy (2000) (**Table 1**), ethanol extracts of the rhizome and aerial parts exerted memory enhancing effects *in vivo*. These effects were associated with increased levels of ChAT and ACh *in vivo*. However, there was no associated increased in AChE inhibitory activity. In another study, an aqueous rhizome extract increased the level of ACh in rat hippocampus, which has been proposed to be due to an increase in ChAT (Rai *et al*. 2002) (**Table 1**).

An ethanol extract obtained from the stem, flowers, leaves and fruits of the plant was reported to be sedative in mice (Kulkarni *et al*. 1988).

Codonopsis pilosula Franch. (Campanulaceae)

C. pilosula (**Plate 1E**), know locally by the name Dang Shen, is a perennial climber which is commonly found in North East Asia. In TCM, the root is used as remedy for amnesia and is believed to improve circulation and increase vitality (Kulkarni *et al*. 1988). An *n*-butanol extract reduced impairment of memory acquisition in mice, induced by scopolamine, cycloheximide and ethanol, respectively. This showed that the extract had nootropic effect (Zhang and Liu 1996).

Convolvulus pluricaulis Chois. (Convolvulaceae)

C. pluriculis, commonly known as Shahkpushpi, is a fulvous hairy herb that has been prescribed by Ayurvedic practitioners for the treatment of nervous disorders and as anti-aging remedy (Kumar 2006). The whole plant in the form of a decoction is used with milk and cumin to treat fever, disability, memory loss, syphilis, and scrofula (Ganju *et al*. 2003).

Coptis chinensis Franch. (Ranunculaceae)

C. chinensis, known commonly as Huang Lian, is an evergreen perennial plant that has been used in TCM for several conditions. In a study carried out by Park *et al*. (1996), dichloromethane and methanol extracts demonstrated AChE inhibitory activity. Shigeta *et al*. (2002) reported that a methanol extract of the rhizome possessed NGF-enhancing activity. Methanol extracts of the plant are reported to have MAO inhibitory activity and nootropic activities *in vivo* and *in vitro* antioxidant activity (Hsieh *et al*. 2000; Kong *et al*. 2001; Schinella *et al*. 2002) (**Table 1**). Liu and Ng (2000) reported that an aqueous extract showed *in vitro* antioxidant activity. An ethanol extract of the whole plant demonstrated anti-inflammatory effect *in vivo* (Cuéllar *et al*. 2001) (**Table 1**).

Crocus sativus L. (Iridaceae)

C. sativus, commonly known as saffron, is small bulbous perennial that has been cultivated throughout the world for its culinary properties. The plant is used in TCM for treating disorders of the nervous system. An alcohol extract of pistils of *C. sativus* and the component crocin improved ethanol-induced impaired learning and behaviour in mice (Sugiura *et al*. 1995a; Abe and Saito 2000) (**Table 1**). This may have been achieved by the inhibiting the impairment of hippocampal synaptic plasticity (Sugiura *et al*. 1995a, 1995b). A hydroalcoholic extract of dried stigmas inhibited Aβ fibrillogenesis and exerted antioxidant effect *in vitro* (Papandreou *et al*. 2006).

Curcuma longa L. (Zingeberaceae)

Rhizomes of *C. longa*, commonly known as turmeric, have been used extensively for their culinary properties in Indian cooking and are used in AM as a remedy against aging. An aqueous extract of the rhizome demonstrated antidepressant activity in mice following oral administration, which was associated with inhibition of brain MAO type A (Yu *et al*. 2002) (**Table 1**). Antidepressant activity is of significant importance in the management of AD.

Evodia rutaecarpa (Juss.) Benth. (Rutaceae)

E. rutaecarpa (**Plate 1F**) is a deciduous small tree that is used in TCM for cardiotonic, restorative and analgesic effects (Howes and Houghton 2003; Howes *et al*. 2003). There are also TCM prescriptions which have been used in CNS disorders. A TCM preparation, Oren-gedoku-to, demonstrated antioxidant (Fushitani *et al*. 1995; Ohta *et al*. 1997; Hayashi *et al*. 2001), anti-inflammatory (Wang and Mineshita 1996; Dai *et al*. 1999; Fukutake *et al*. 2000) and neuroprotective (Kabuto *et al*. 1997; Kondo *et al*. 2000) activities. However, there are TCM preparations of the plant which, despite their claim failed to improve declining memory. An example is NaO Li Su which, failed to improve cognitive dysfunction in a double blind placebo controlled crossover trial (Iversen *et al*. 1997).

A dichloromethane extract of *E. rutaecarpa* strongly inhibited AChE *in vitro* and reversed scopolamine-induced memory impairment in rats (Park *et al*. 1996) (**Table 1**).

Ginkgo biloba L. (Ginkgoaceae)

G. biloba (**Plate 2A**) is dioecious perennial tree that is indigenous to East Asia, that has been used in TCM for the improvement of memory loss associated with abnormalities in the blood circulation (Samuelsson 2004b). Administration of plant extracts to both AD and non-AD patients in various randomised, double-blind, placebo controlled, multicentre trials resulted in improvement of cognitive functions (Hofferberth 1994; Kanowski *et al*. 1997; le Bars *et al*. 1997; Rigney *et al*. 1999) (**Table 1**).

Since early pharmacological studies revealed that the flavonoids from *G. biloba* modulated contractile motion of vascular smooth muscles, attempts were made to prepare a standardised extract rich in flavonoids, the outcome of which is EGb 761 (Kumar 2006). EGb 761 showed cognitive enhancing activity in number of clinical studies (Hofferberth 1994; le Bars *et al*. 1997; Maurer *et al*. 1997; Kanowski *et al*. 1997) (**Table 1**). The extract showed neuroprotective effect against Aβ and nitric oxide (NO) induced toxicity in the neuronal cell culture (Bastianetto *et al*. 2000a, 2000b) and could reduce apoptosis both *in vitro* and *in vivo* (Schindowski *et al*. 2001; Yao *et al*. 2001) (**Table 1**). EGb 761 showed protective effect against ischaemia-induced neurotoxicity (Chandrasekaran *et al*. 2001). The extract also demonstrated *in vitro* and *in vivo* antioxidant activities (Barth *et al*. 1991; Marcocci *et al*. 1994; Topic *et al*. 2002). The extract improved blood supply to the brain, thereby ensuring its efficient functioning and enhanced cognitive performance (Heiss and Zeiler 1978; Loffler *et al*. 2001) (**Table 1**). Modulation of muscarinic cholinergic system enhanced performance of spatial task (Kristofiková *et al*. 1992).

Hypericum perforatum L. (Clusiaceae) (Hypericaceae)

H. perforatum (**Plate 2B**) commonly known as St. John's Wort is a herbaceous perennial plant that has been used in Portuguese and Turkinsh folklore medicine for the treatment of neurological disorders (Ross 2001). The dried crude herb standardised to hypericins improved memory and learning dysfunction (Widy-Tyszkiewicz *et al*. 2002; Trofimiuk *et al*. 2005) (**Table 1**). Lu *et al*. (2001) reported that a standard extract of *H. perforatum* (hypericin) possessed neuroprotective activity. It is reported that extracts of *H. perforatum*, which have been standardised to hypericin and hyperforin respectively, showed *in vitro* antioxidant activity (Hunt *et al*. 2001; Zheng and Wang 2001), *in vivo* anti-inflammatory effects (Kumar *et al*. 2001).

Hydroalcoholic extracts of aerial parts of *H. perforatum*,

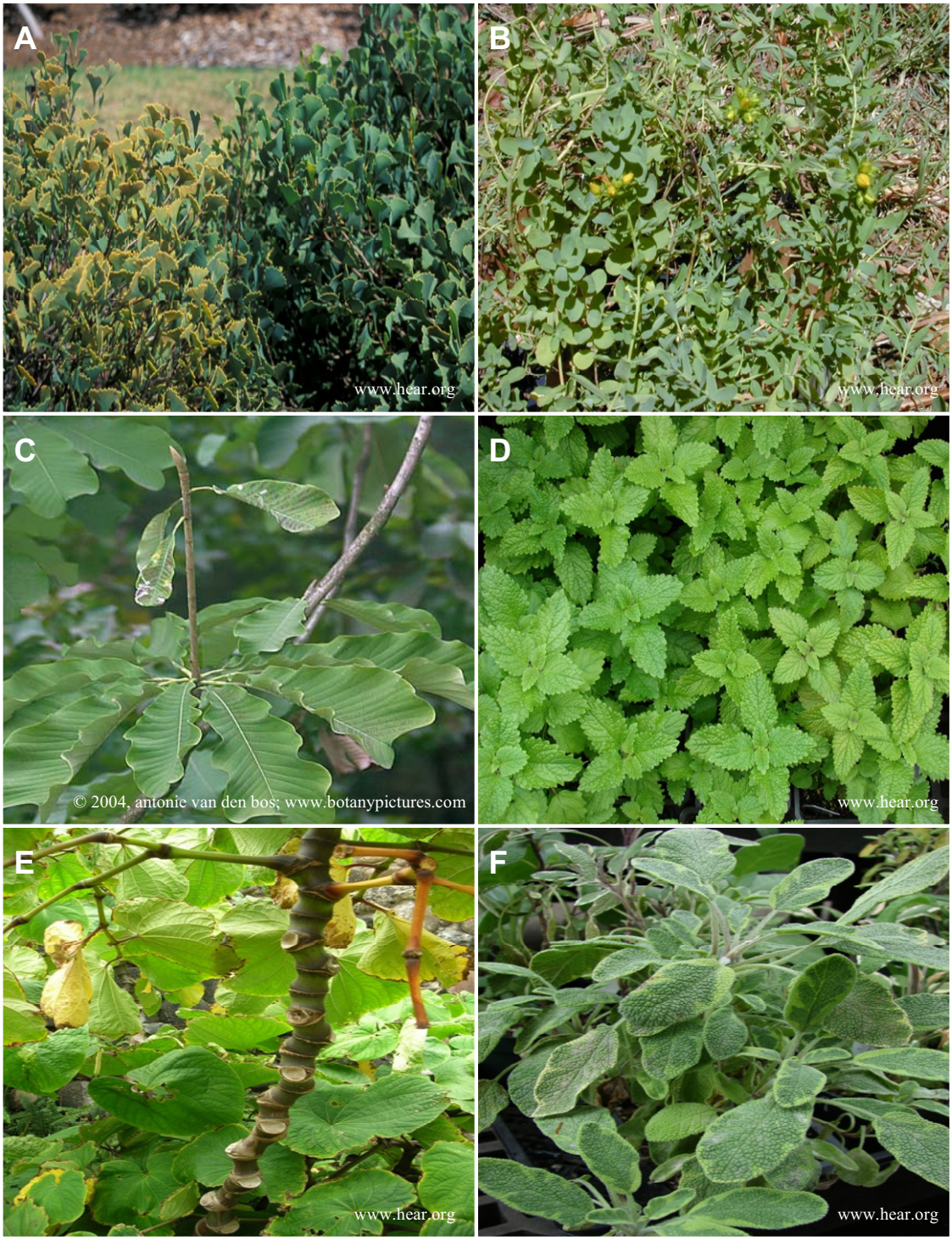

Plate 2 Aerial parts of (**A**) *Ginko biloba* L.; (**B**) *Hypericum perforatum* L.; (**C**) *Magnolia officinalis* var. biloba Rehd.& Wils.; (**D**) *Melissa officinalis* L.; (**E**) *Piper methysticum* Frost. and (**F**) *Salvia officinalis* L.

demonstrated nootropic activity *in vivo*, which may due to adrenergic (α and β receptor) and serotonergic (5HT1A) antagonistic activity (Khalifa 2001; Kumar *et al*. 2002c, 2000) (**Table 1**). Re *et al*. (2003) suggested that a hydroalcoholic extract of the plant could reduce the rate of degradation of ACh.

Magnolia officinalis Rehd. & Wils. (Magnoliaceae)

M. officinalis (**Plate 2C**) is a deciduous tree originally from East Asia that has been used in TCM for treating nervous disorders. Ethanolic extract of *M. officinalis*, magnolol and honokiol are reported to have antioxidant activity *in vitro* and *in vivo* (Lo *et al*. 1994; Chiu *et al*. 1997; Jie *et al*. 2000; Kong *et al*. 2000; Chen *et al*. 2001). Li and Weng (2005) demonstrated the *in vitro* antioxidant activity of various Soxhlet and supercritical fluid extracts, with the ethyl acetate-soluble Soxhlet extract being the most active.

Melissa officinalis L. (Lamiaceae)

M. officinalis (**Plate 2D**), commonly known as lemon balm, is a perennial herb native of West Asia and eastern Mediterranean region that has been used in the European traditional system of medicine as a remedy for improving memory (Bisset 1994; Perry *et al*. 1996; Howes *et al*. 2003). The volatile oil has been reported to possess *in vitro* AChE inhibitory (Perry *et al*. 1996; Ferreira *et al*. 2006) and antioxidant activities (Mimica-Dukic *et al*. 2004; de Sousa *et al*. 2004; Ferreira *et al*. 2006). Its constituent monoterpenes were reported to possess weak AChE inhibitory activity (Ryan and Byrne 1988), while it has been suggested its anti-

oxidant activity is due to presence of oxygenated monoterpenes and sesquiterpene hydrocarbons (Mimica-Dukic *et al*. 2004).

A wide range non-polar and polar extracts have displayed antioxidant activity (Triantaphyllou *et al*. 2001; Marongiu *et al*. 2004; Venskutonis *et al*. 2005; Ivanova *et al*. 2005; Ferreira *et al*. 2006; Dastmalchi *et al*. 2008). In case of polar extracts, it has been proposed that the active constituents contributing to the activity of the extracts are the polyphenolic substances (Ivanova *et al*. 2005; Dastmalchi *et al*. 2008).

Ethanol and decoction extracts of aerial parts of the plant also showed *in vitro* AChE inhibitory activity (Ferreira *et al*. 2006). Ethanol extracts obtained from the leaf material were reported possessed nicotine and muscarinic receptor binding properties (Perry *et al*. 1996; Wake *et al*. 2000). A methanolic extract of the plant leaves was clinically capable of improving the mood and accuracy of attention Kennedy *et al*. (2002) (**Table 1**). However, there was a decline in memory function. Furthermore, *in vitro* nicotinic and muscarinic binding were low in comparison to that found by Wake *et al*. (2000). This difference may be due to loss of volatile component during the manufacturing process (Wake *et al*. 2000). Based on the reports of Kennedy *et al*. (2002) and Wake *et al*. (2000), a clinical study was conducted by Akhondzadeh *et al*. (2003a) in which, a hydro-alcoholic leaf extract was effective in improving cognitive functions in mild to moderate AD patients (**Table 1**).

Piper methysticum Frost. (Piperaceae)

P. methysticum (**Plate 2E**), commonly known as Kava, is a perennial shrub that has been used in Polynesia, Melanasia and Micronesia occupies in preparation of a drink to be consumed for ritual and social purposes (Samuelsson 2004c; Shinomiya 2005). In a clinical trial carried out by Thompson *et al*. (2004) (**Table 1**), a standardised rhizome extract (kavalactones) elevated the mood and enhanced cognition performance.

Polygala tenuifolia Wild. (Polygalaceae)

P. tenuifolia, commonly know as Senega, is a perennial herb, which according to the *Chinese Materia Medica* its rhizome has been used as a sedative, tranquiliser and for the treatment of amnesia, forgetfulness, neuritis, nightmares and insomnia (Duke and Ayensu 1985). There have been many studies carried out on the preparation used in TCM containing *P. tenuifolia* one of which is DX-9386. This formulation demonstrated *in vivo* antioxidant activity, and improved memory dysfunction in mice (Nishiyama *et al*. 1994a, 1994b, 1994c; Zhang *et al*. 1994).

P. tenuifolia is also a component of Kami-utan-to (KUT), a traditional Japanese preparation used in the treatment of psychoneurological diseases. KUT up-regulated ChAT activity and increased NGF secretion *in vitro*, it also induced ChAT activity in the cerebral cortex of aged rats and in the scopolamine induced memory impaired rats (Yabe *et al*. 1997; Yamada and Yabe 1997). The effect of the preparation in up regulation of ChAT activity and increased NGF secretion was not as significant when *P. tenuifolia* was absent, however, the rhizome extract did not contribute to the effects (Yabe *et al*. 1997; Yamada and Yabe 1997). It was demonstrated in a clinical study that KUT treatment in AD patients improved memory-related behaviour (Yamada and Yabe 1997). It is suggested that, cinnamic acid derivatives may be contributing to the beneficial effects of KUT (Yabe *et al*. 1997).

A dichloromethane subfraction of a methanol rhizome extract demonstrated *in vitro* AChE inhibitory activity (Park *et al*. 1996). In another study, an ethanol rhizome extract improved cognitive dysfunction, and exerted protective effect against glutamate and APP toxic metabolites induced neurotoxicity *in vitro* (Park *et al*. 2002) (**Table 1**).

Aqueous extract of the rhizome showed *in vitro* anti-inflammatory properties (Kim *et al*. 1998; Koo *et al*. 2000). The aqueous extract also demonstrated tranquilizing activity (Tang and Eisenbrand 1992; Chang and But 2001).

Rheum spp. L. (Polygonaceae)

It is usually common to refer to *Rheum palmatum* L. and other species and hybrids of the genus *Rheum*, except *Rheum rhaponticum*, as rhubarb (Samuelsson 2004d). The dried rhizome of rhubarb has been used in TCM for the treatment of blood stagnation syndrome (Matsuda *et al*. 2001).

In a study carried out by Kageura *et al*. (2001), a methanol extract obtained from the rhizome of Korean rhubarb, *Rheum undulatum*, demonstrated *in vitro* antioxidant activity. In another study, methanol extracts of rhizomes from five *Rheum* species (*R. palmatum*, *R. tanguticum*, *R. officinale*, *R. coreanum* and *R. undulatum*) exhibited *in vitro* antioxidant properties (Matsuda *et al*. 2001).

Salvia lavandulaefolia Vahl. (Lamiaceae)

S. lavandulaefolia, known by the common name Spanish Sage, is a perennial shrub which along with *Salvia officinalis* has been used in European traditional medicine for enhancement of memory (Perry *et al*. 1998).

Volatile oil obtained from *S. lavandulaefolia* showed strong AChE inhibitory activity (Perry *et al*. 1996). The activity is believed to be due to the presence of the cyclic monoterpenes 1,8-cineole and α-pinene, with some contribution from other constituents perhaps by acting synergistically (Perry *et al*. 2001). Administration of *S. lavandulaefolia* volatile oil decreased AChE activity *in vivo* (Perry *et al*. 2001). Components of the oil were also screened for antioxidant activity. 1,8-Cineole, α-pinene and β-pinene exerted antioxidant effect, however, camphor showed pro-oxidant activity (Perry *et al*. 2001).

The ethanol *S. lavandulaefolia* extract showed weak activity when compared against antioxidant propyl gallate. Water and chloroform subfractions of this extract demonstrated similar activity (Perry *et al*. 2001). An ethanol extract of the plant demonstrated *in vitro* anti-inflammatory properties (Perry *et al*. 2001). In a clinical study carried out by Tildesley *et al*. (2005) (**Table 1**), administration of a standardised essential oil extract resulted in mood elevation and improvements of memory.

Salvia miltiorrhizia Bung. (Lamiaceae)

S. miltiorrhiza (**Plate 2F**), commonly known as Dan-Shen, is a perennial herb which its rhizomes have been used for the treatment of diseases and pathological conditions such as cardiovascular disorders, insomnia, neurasthenia, inflammation (Tang and Eisenbrand 1992; Huang 1993).

Moon *et al*. (1998) reported that a methanol extract of the plant demonstrated *in vitro* anti-inflammatory activity. The extract was fractionated further and among all the fractions ethyl acetate fraction displayed the strongest anti-inflammatory activity. In a study carried out by Hsieh *et al*. (2000) (**Table 1**), the methanol extract improved cognitive dysfunction in rats.

Aqueous leaf and rhizome extracts of the plant, demonstrated *in vitro* antioxidant properties (Koo *et al*. 2004; Zhao *et al*. 2006).

Salvia officinalis L. (Lamiaceae)

S. officinalis is a perennial shrub native of Mediterranean region, and is believed by many to be the plant sage which has a reputation in the European and other traditional and folklore medicine for promoting intellect (Perry *et al*. 1998). Essential oil obtained from the plant exhibited *in vitro* AChE and BuChE inhibitory activities (Perry *et al*. 1996; Savelev *et al*. 2004).

Eun-A *et al*. (2004) reported that hexane and ethyl ace-

tate extracts of the plant showed *in vitro* anti-inflammatory properties. In another study hexane and chloroform extracts of the leaves were reported to possess *in vivo* anti-inflammatory activity (Baricevic *et al*. 2001) (**Table 1**). Miliauskas *et al*. (2004) demonstrated that ethyl acetate, acetone extracts obtained from the aerial parts of the plant possessed *in vitro* antioxidant properties.

Methanol extracts of the leaf material and the aerial parts also showed *in vitro* antioxidant activity (Hohmann *et al*. 1999; Pizzale *et al*. 2000). Ethanolic leaf extract of *S. officinalis* demonstrated *in vitro* AChE and BuChE inhibitory activities (Perry *et al*. 1996; Kennedy *et al*. 2006). A hydroalcoholic extract form the leaves demonstrated *in vitro* protective effect against Aβ induced neurotoxicity (Iuvone *et al*. 2006). In a clinical study carried out by Akhondzadeh *et al*. (2003b) (**Table 1**), a hydroalcoholic leaf extract was effective in the management of mild to moderate AD. Aqueous extracts of the leaves, obtained by hydrodistillation and hot water extraction displayed *in vitro* antioxidant activity (Ollanketo *et al*. 2002; Dorman *et al*. 2003).

Terminalia chebula L. (Combretaceae)

The ripe fruit of *T. chebula* is reputed to enhance memory and to promote longevity (Misra 1998; Manyam 1999). However, there is no hard data substantiating the reputed effects of this plant in the AM. A methanol extract is reported to bind NMDA and GABA receptors, but did not show any cholinesterase inhibitory activity (Dev 1997). In a study carried out by Naik *et al*. (2004), the aqueous extract of dried fruits *T. chebula* demonstrated *in vitro* antioxidant activity.

Withania somnifera L. (Solonaceae)

The root of the plant *W. somnifera* known by the name Ashwagandha is one of the most valuable herbs used in AM. It is used rejuvenative tonics ('Rasyanas'), and enhancement of memory and intellect in AM (Upton 2000).

Administration of the standardised root extracts improved cognitive dysfunction *in vivo* (Dhuley 2001; Naidu *et al*. 2006) (**Table 1**). A hydroalcoholic extract of the roots standardised for withanolides and withanoles showed neuroprotective effect *in vivo* (Jain *et al*. 2001) (**Table 1**). Hydroalcoholic and ethanolic root extracts demonstrated *in vitro* and *in vivo* antioxidant and anti-inflammatory properties (Dhuley 1997; Chaurasia *et al*. 2000; Gacche and Dhole 2006) (**Table 1**).

A methanol root extract promoted the formation of dendrites in a culture of human neuroblastoma cells (Tohda *et al*. 2000). Bhatnagar *et al*. (2005) reported that the methanolic extract possessed *in vivo* antioxidant properties.

W. somnifera root powder demonstrated *in vivo* antioxidant and anti-inflammatory effects (Rasool and Varalakshmi 2007) (**Table 1**).

PHYTOCHEMICALS

Arecoline

The alkaloid arecoline is isolated from the betel nut of *Areca catechu* L. (Aracaceae), which is used as a masticatory throughout the Indian subcontinent and other parts of southeast Asia. Administration of arecoline resulted in improvement of memory in rats (Bratt *et al*. 1996). Arecoline has exhibited muscarinic (M_2) binding activity (Yang *et al*. 2000). In a clinical study arecoline demonstrated memory enhancing effect in AD patients (Soncrant *et al*. 1993). Despite initial success with *in vitro* studies the compounds failed to improve the cognitive functions in mild to moderate AD patients (Houghton and Howes 2005). However, research on synthetic analogue of arecoline such as Lu 25-109 (**24**) and talsaclidine (**25**) appears to be promising (Houghton and Howes 2005).

Asiaticosides

Lee *et al*. (2000) reported the triterpene Asiatic acid (**26**) and its derivatives protected cortical neuronal cell against glutamate induced toxicity *in vitro*. Asiaticoside derivatives were assessed *in vitro* for their neuroprotective activity against β-amyloid toxicity death (Mook-Jung *et al*. 1999). Of 28 asiaticoside derivatives, three components including Asiatic acid and its derivatives, showed strong inhibition of β-amyloid and free radical-induced cell death (Mook-Jung *et al*. 1999). These derivatives may potentially be candidates in AD treatment.

Bacosides

Bacosides, which are dammarane triterpenoid saponins isolated from *Bacopa monniera*, showed nootropic activity (Russo and Borrelli 2005; Kumar 2006). These compounds such as bacoside A(3) (**27**), demonstrated *in vitro* antioxidant activity (Pawar *et al*. 2001).

Biphenolic lignans

Biphenolic lignans isolated from *Magnolia officinalis*, honokiol (**28**) and magnolol (**29**), have demonstrated the ability to increase ChAT activity and inhibit AChE activity *in vitro* and have also shown to release hippocampal ACh *in vivo* (Hou *et al*. 2000). Both the compounds showed *in vivo* antioxidant activities (Lo *et al*. 1994).

Magnolol demonstrated *in vitro* neuroprotective effect (Lee *et al*. 1998). The compound also showed anti-inflammatory activity *in vitro* and *in vivo* (Wang *et al*. 1992, 1995).

Liou *et al*. (2003) demonstrated that honkiol exerted *in vivo* anti-inflammatory effect by inhibiting ROS formation.

Caffeic acid derivatives

Salvianolic acids A (**30**) and B (**31**) isolated from *Salvia miltiorrhiza* offered protection against cerebral ischemia induced memory impairment in mice (Du and Zhang; 1997 Du *et al*. 2000). Lin *et al*. (2006) reported that salvianolic acid B prevented Aβ (25-35) induced neurotoxi-city *in vitro*. This effect was accompanied by decreased formation ROS, suggesting the antioxidant activity being behind the neuroprotective effect. Rosmarinic (**32**) a well known antioxidant isolated from *Salvia* and other Lamiaceae species (Jiang *et al*. 2005; Imanshahidi *et al*. 2006; Dastmalchi *et al*. 2008) demonstrated *in vitro* protective effect against Aβ induced neurotoxicity (Iuvone *et al*. 2006).

Sinapic acid (**33**) isolated from *Polygala tenuifolia* increased the activity of ChAT in the frontal cortex of brain lesioned rats (Yabe *et al*. 1997).

Crocin

Crocin (**34**) isolated from *Crocus sativus* demonstrated cognitive enhancing activity in mice (Sugiura *et al*. 1995a; Abe and Saito 2000). The compound possessed *in vitro* antioxidant and antiamyloidogenic properties (Papandreou *et al*. 2006), furthermore it suppressed TNF-α-induced apoptosis *in vitro* (Soeda *et al*. 2001).

Curcuminoids

Curcuminoids from *Curcuma longa*; curcumin (**35**), demethoxycurcumin (**36**), bisdemethoxycurcumin (**37**) and calebin-A (**38**) (and some of its synthetic analogues), showed neuroprotective activity against Aβ-induced toxicity (Kim and Kim 2001; Park and Kim 2002). It was suggested that this activity may be due to an antioxidant effect (Kim *et al*. 2001). Among the curcuminoids present in *C. longa*, curcumin has been the subject of most research (Xu *et al*. 2006).

The antioxidant activity of curcumin has been reported in various studies (Priyadarsini 1997; Scartezzini and Speroni 2000; Das and Das 2002; Miquel *et al*. 2002). It de-

monstrated neuroprotective activity against ethanol-induced brain injury *in vivo*. It was reported that this effect was related to its *in vivo* antioxidant activity (Rajakrishnan *et al*. 1999). A number of studies have demonstrated that curcumin possesses anti-inflammatory activity (Srivastava *et al*. 1995; Ramsewak *et al*. 2000; Skrzypczak-Jankun *et al*. 2000; Miquel *et al*. 2002). Using computational software Balasubramanian (2006) demonstrated that curcumin as a result of containing an enolic centre and two phenolic polar groups separated by a conjugated hydrocarbon chain, exhibits its unique hydrophobic and hydrophilic features. The former property facilitates its partition into the blood brain barrier and the later enables its binding to the Aβ peptide. Further studies also show that the enol isomer has all the properties for an ideal antioxidant.

Galantamine

The alkaloid galantamine is found in members of Amaryllidaceae family including the Chinese medicinal plant *Lycoris radiata* Herb. and the European *Gallantus nivalis* Herb. and *Narcissus* spp. Galantamine is licensed in Europe for AD treatment and has been reported to significantly improve the cognitive functions when administered to the patients in multicentre randomised clinical trials (Wilcok *et al*. 2000; Wilkinson and Murray 2001). This alkaloid, which is also isolated from is shown to be more selective inhibitor for AChE than BuChE and provide complete oral bioavailability (Bickel *et al*. 1991; Harvey 1995; Fulton and Benfield 1996). The alkaloid is also capable of stimulating nicotinic receptors which is believed to further enhance cognition and memory (Pearson 2001; Woodruff-Pak *et al*. 2001). This is a therapeutic advantage over that of other AChE inhibitors.

Clinical studies have also shown that the alkaloid improves the symptoms of cerebral haemorrhage induced hemiplagia (Chang and But 2001). This may be of value in vascular dementias.

Huperzine A

Huperzine A (**39**), a quinolizindine alkaloid isolated from *Huperzia serrata* Brenh. (Lycopodiaceae), has demonstrated in a number of *in vitro* and *in vivo* studies its ability to reversibly inhibit AChE (Wang *et al*. 1986; Laganiére *et al*. 1991; McKinney *et al*. 1991; Ashani *et al*. 1992).

In a number of animal studies, administration of the alkaloid showed it has improved working and spatial memory (Lu *et al*. 1988; Xiong and Tang 1995; Wang and Tang 1998; Ye *et al*. 1999; Wang *et al*. 2000; Lian *et al*. 2001). Huperzine A improved cognitive functions in chronically hypoperfused rats (Wang *et al*. 2000) and in gebrils following ischaemia (Zhou *et al*. 2001a, 2001b). It is suggested that the cerebrovascular effects of the extract may be contributing to cognitive enhancing action.

In a double blind clinical trial Huperzine A improved behaviour and memory in AD patients, and it was more selective for acetylcholinesterase (AChE) than butyrylcholinesterase (BuCheE) (Small *et al*. 1997; Shu 1998). The alkaloid was less toxic than the synthetic cholinesterase inhibitors such as tacrine and donepezil.

Huperzine A extracts have been shown to have neuroprotective activity against Aβ2335-induced neurotoxicity (Xiao *et al*. 2002), scavenge free radicals (Xiao *et al*. 1999) and possess antagonistic NMDA receptor activity in the cerebral cortex (Wang *et al*. 1999). Zhou and Tang (2002) reported that huperzine A also inhibited apoptosis by modulating the mitochondrial caspase pathway. This compound has currently been introduced in China for the management of AD patients, while phase II clinical studies are being conducted in US.

Hyperforine

The vast majority of the reports on the pharmacological uses of the plant extracts and their therapeutic potential revolves around the phytochemical constituents hyperforine (**40**) (Kumar *et al*. 2000; Lu *et al*. 2001; Widy-Tyszkiewicz *et al*. 2002; Kumar *et al*. 2002c; Trofimiuk *et al*. 2005; Kumar 2006). The phytochemical substance is also reported to possess NMDA receptor antagonistic activity, thereby inhibiting glutamate induced neurotoxiciy (Kumar 2006). In a study carried out by Klusa *et al*. (2001) hyperforin completely reversed scopolamine-induced amnesia in mice, thereby showing its cognitive enhancing action.

Pilocarpine

The alkaloid pilocarapine is isolated from the species belonging to the plant genus *Pilocarpus* found mainly in South America. The molecular structure of the alkaloid bears similarities with ACh since the positively charged N atom and the lactone binding to the serine are the same distance apart and this is proposed to be the reason behind its muscarinic binding activity (Houghton and Howes 2005). The alkaloid has demonstrated nootropic activity in the rat (Levin and Torry 1996); however, no studies have been done in humans due to its poor pharmacokinetic profile (Houghton and Howes 2005).

Protoberberine alkaloids

Shigeta *et al*. (2002) reported that alkaloids berberine (**41**), coptisine (**42**) and palmatine (**43**) isolated from *Coptis chinesis* possessed AChE inhibitory and NGF-enhancing activities *in vitro*.

Stilbenes

Resveratrol (**44**), rhaponticin (**45**) and rhapontigenin (**46**) isolated from rhubarb demonstrated *in vitro* neuroprotective action against Aβ induced toxicity (Misiti *et al*. 2006), furthermore these compound possessed *in vitro* antioxidant properties (Kageura *et al*. 2001; Matsuda *et al*. 2001). Resveratrol inhibited Aβ fibril formation (Rivière *et al*. 2007) and promoted Aβ clearance *in vitro* (Marambaud *et al*. 2005). The compound improved cognitive dysfunction, which is proposed to be related to its *in vivo* antioxidant and AChE inhibitory activities. (Sharma and Gupta 2002; Luo and Huang 2006).

Tanshinones

Tanshinones isolated from *S. miltiorrhiza*, viz., tanshinone I (**47**), dihydrotanshinone (**48**), methylenetanshiquinone (**49**) and cryptotanshinone (**50**), demonstrated significant antioxidant effect in lard (Zhang *et al*. 1990; Weng and Gordon 1992). Tanshinon I, dihydrotanshinone, and cryptotanshinone showed anti-inflammatory activity *in vitro* and *in vivo* (Kang *et al*. 2000; Kim *et al*. 2002).

Ren *et al*. (2004) demonstrated that tanshinone I and tanshinone IIA (**51**), dihydrotanshinone, cryptotanshinone, exerted AChE inhibitory activity *in vitro*. Tanshinone improved changes induced by Aβ (1-42) in rats, including a decrease in AChE positive fibres (Li *et al*. 2004).

A screening method based on Aβ induced neurotoxicity, have been used to identify Aβ-peptide inhibitor, tanshinone IIA (Hu *et al*. 2007). Both the screening method and the inhibitor have been patented in China (Hu *et al*. 2007).

Tanshinones followed demonstrated a wide range of pharmacological activities of relevance to AD therapy, therefore they are potential targets for further drug discovery studies. The fact that tanshinone IIA has already been patented shows research on *S. miltiorrhizia* has proved promising.

Terpenoid indole alkaloid

Dehydroevodiamine (**52**) strongly inhibited AChE *in vitro* and reversed scopolamine-induced memory impairment in

rats (Park *et al*. 1996). Dehydroevodiamine increased cerebral blood flow *in vivo*, which may contribute to the nootropic activity of the compound (Haji *et al*. 1994). Rutaecarpine (**53**), isolated from *E. rutaecarpa* inhibited COX-2 activity *in vitro*, and exerted anti-inflammatory effect *in vivo* (Matsuda *et al*. 1998; Moon *et al*. 1999).

Terpenoid trilactones

In addition to flavonoids, there are terpene lactones, i.e. bilobalide (**54**) and ginkgolides present in *Ginkgo bilolba*, that have been classified as nootropic agents (Kumar 2006). Some of the research showed that bilobalide, was successful in inhibiting phospholipids breakdown and cholinesterase release under hypoxic conditions (Klein *et al*. 1997). This group has also established that bilobalide inhibited glutamatergic excitotoxic membrane breakdown both *in vivo* and *in vitro*, an effect of great relevance to neuronal hyperactivity and neurodegeneration (Weichel *et al*. 1999). Recently another group has reported that bilobalide inhibited an NMDA-induced chloride flux through glycine/GABA-operated channels, thereby preventing NMDA induced breakdown of membrane phospholipids (Klein *et al*. 2003). Bilobalide showed protective effect against ischaemia-induced neurotoxicity (Chandrasekaran *et al*. 2001).

Wu *et al*. (2006) reported that ginkgolides alleviates Aβ induced pathological behaviour. Ginkgolide B (**55**) demonstrated neuroprotective activity against Aβ induced toxicity (Bate *et al*. 2004). Ginkgolides also reversed Aβ suppression of ACh release *in vivo* (Lee *et al*. 2004).

It should be mentioned that despite the structural similarities between ginkgolides and bilobalide, few analogies between their CNS activities profiles can be detected (Kumar 2006). In a structure activity study, Chatterjee *et al*. (2003) have indicated that the difference in the existing molecular space around the (*tert*-butylated substituted cyclopentane ring) dictate their activity profile (Chatterjee *et al*. 2003).

Withanolides

There have been numerous studies on *W. somnifera* and its constituents. The sitoindosides IX (**56**) and X (**57**) isolated from the plant, augmented learning acquisition and memory in both young and old rats (Ghosal *et al*. 1989).

It has been suggested that the mechanism for this effect may involve modulation of cholinergic neurotransmission. Administration of a mixture containing sitoindosides VIII-X and withaferin A (**58**) to mice resulted in enhanced AChE activity in the lateral septum and globus pallidus and decreased AChE activity in the vertical diagonal band, enhanced muscarinic M_1 receptor binding in the lateral and medial septum and in frontal cortices, and increased muscarinic M_2 receptor binding sites in the cortical regions (Schliebs *et al*. 1997). The mixture improved ibotenic acid-induced cognitive dysfunction and reduction in the cholinergic markers in rats (Bhattacharya and Kumar 1995). The compounds glycowithanolides and sitoindosides are believed to be responsible for antioxidant activity of *W. somnifera* because they demonstrated their effect both *in vitro and in vivo* (Bhattacharya *et al*. 1997; Chaurasia *et al*. 2000; Bhattacharya *et al*. 2001b).

Zeatin

*Z*eatin (**59**), isolated from *F. villosa*, exerted AChE inhibitory effect *in vitro* (Letham *et al*. 1967; Hoe *et al*. 2002).

CONCLUSION

By looking at the pharmacological activities of the plant extracts investigated it can be concluded that essential oils and non-polar extracts of a wide range of plant species such as *Angelica archangelica*, *Centella asiatica*, *Celastrus paniculatus*, *Coptis chinensis*, *Evodia rutacarpa*, *Melissa officinalis*, *Polygala tenuifolia*, *Salvia officinalis*, *Salvia lavandulaefolia and Salvia miltiorrhiza* at differing dosages demonstrated AChE inhibitory activity. The extracts were prepared from the rhizome, seeds and aerial parts of the plants, however in some cases the plant parts used in the extraction were not specified. In few cases the phytochemical constituents contributing to the activity have been isolated. These include alkaloids, monoterpenes, diterpenes and triterpenoids. The non polar extracts and essential oils from *C. asiatica*, *Melissa officinalis* and *Salvia* species possessed antioxidant and anti-inflammatory properties. However, some of the phytochemicals responsible for the activities of the extracts have not been identified, therefore, it is suggested that the extracts be subjected to activity guided fractionation. It is also proposed that the compounds, which have already been isolated to be investigated further in models of AD.

Another interesting trend is that the polar extracts of the plant species mentioned above and other medicinal plants showed antioxidant and anti-inflammatory activities. It has been proposed that the activities are due to the presence of flavonoids, cinnamic acid derivatives, triterpenoid saponins, bacosides, curcuminoids, zeatin, crocin, anthraquinone glycosides, dimeric anthraquinone derivatives, phloroglucinol derivatives, naphathalene glucosides and stilbenes.

There are some standardised extracts which have proven to be effective in the clinical studies and currently they are being investigated for their pharmacodynamic and pharmacokinetic properties. The *Ginkgo biloba* extract EGB 761, and hypericum extract are such examples.

Based on phytochemical and pharmacological studies carried out there are several phytoconstituents which can be potential drug targets for AD treatment. These include asiatic acid, berberine, coptisisne, palmitine, crocin, rutacarpine, dehydroevodiamine, curcumin, hyperforin, hypericin, honokiol, magnolol, sinapic acid, rhaponticin, rhapontigenin, resveratrol, tanshinones, salvianolic acids, arecoline and pilocarpine. However there are some phytochemical substance which have already been launched or in the clinical trial phase. It should be also mentioned that these substances, examples of which galantamine and huperzine A are only being used in the management of AD patients.

Therefore, one can conclude that extracts of medicinal plants having a wide range of polarity and different classes of phytochemical substances have demonstrated pharmacological activities relevant to the treatment of AD.

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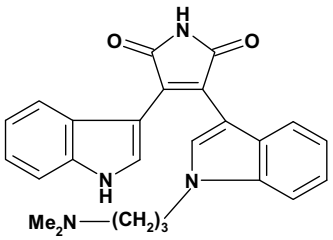

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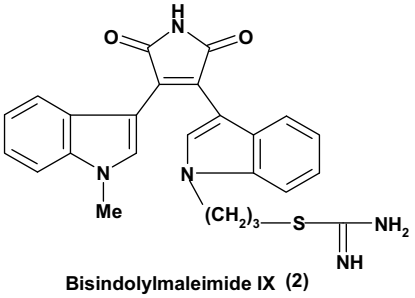

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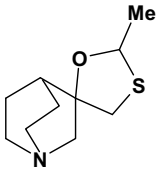

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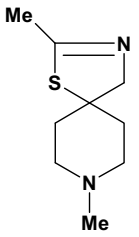

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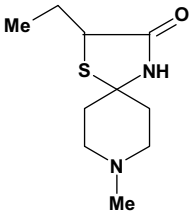

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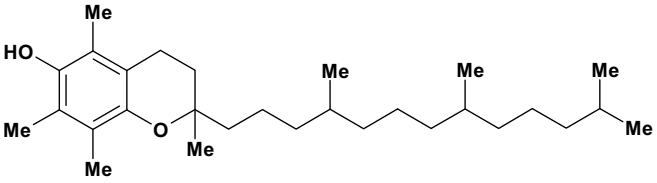

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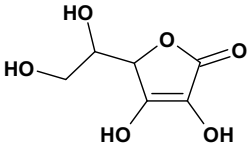

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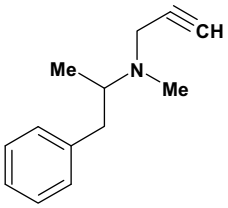

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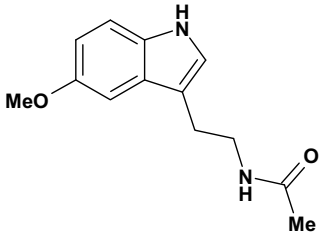

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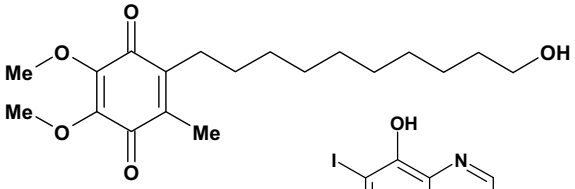

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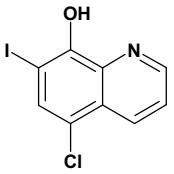

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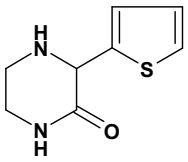

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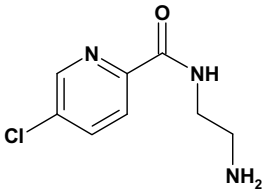

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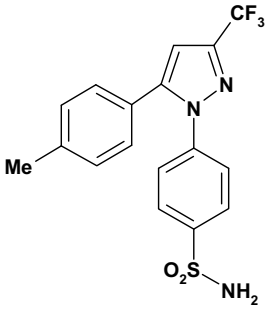

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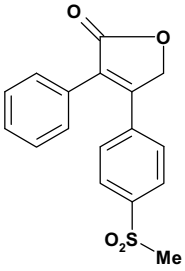

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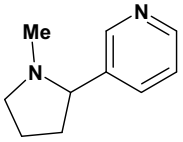

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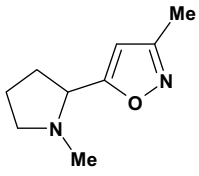

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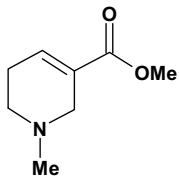

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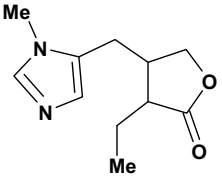

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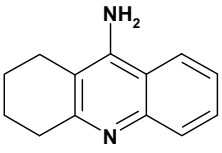

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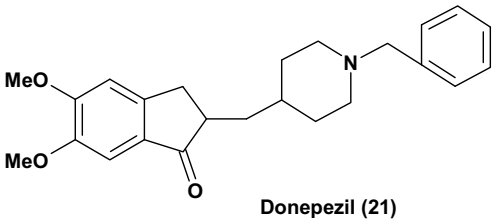

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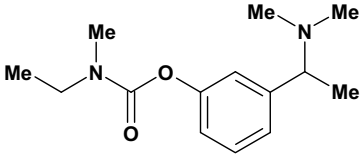

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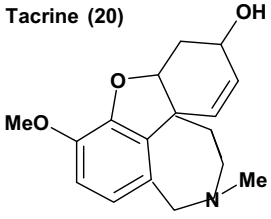

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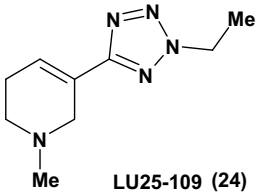

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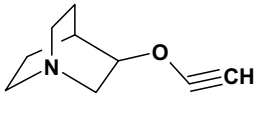

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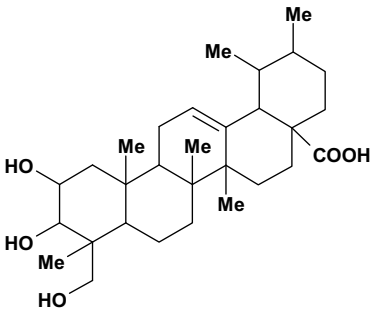

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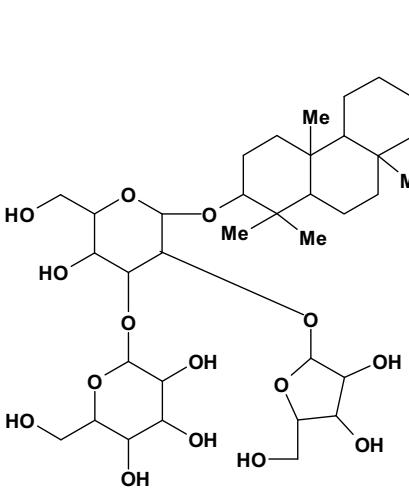

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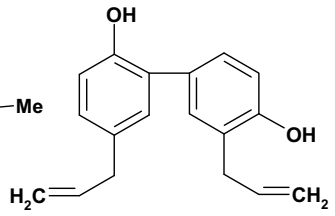

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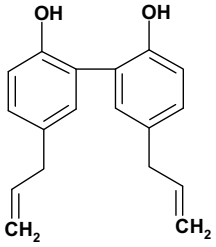

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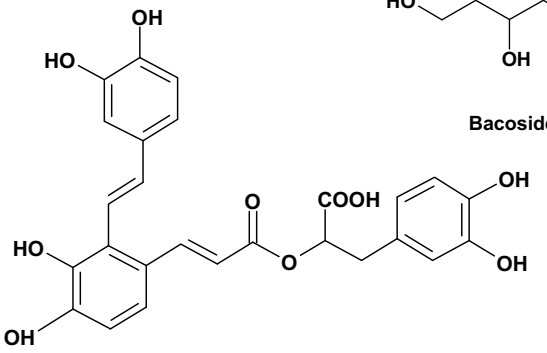

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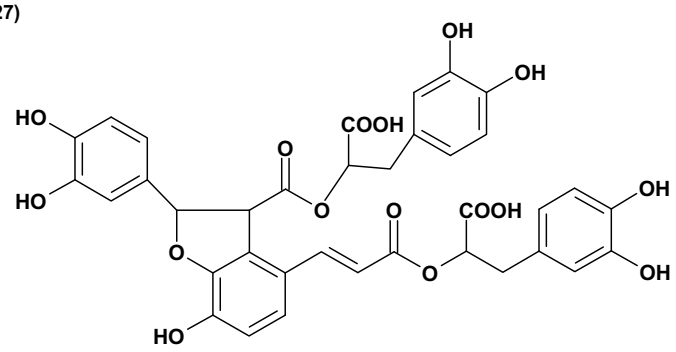

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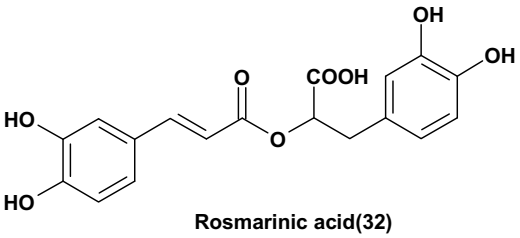

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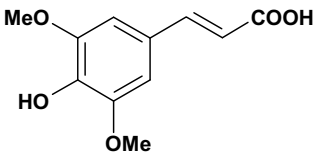

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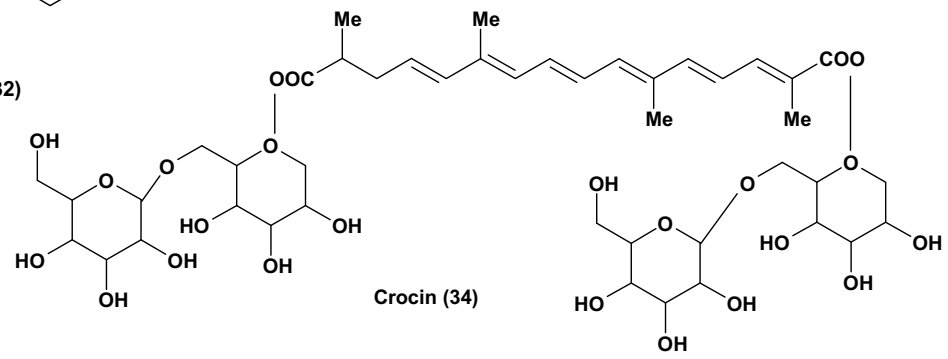
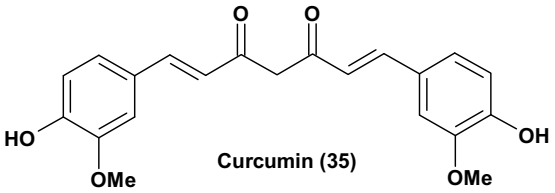
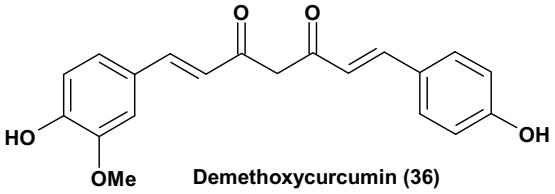


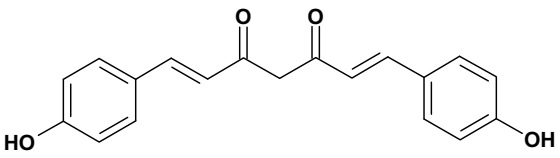
Crocin (34)



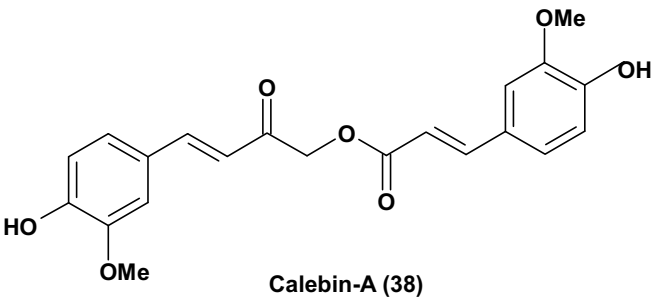
Curcumin (35)



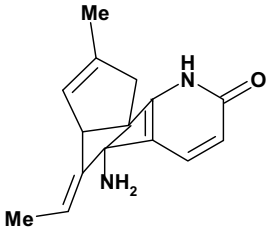
Demethoxycurcumin (36)



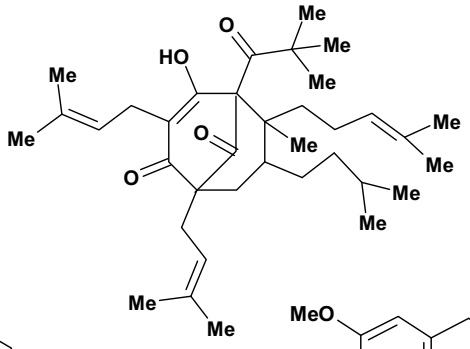
bisdemethoxycurcumin (37)



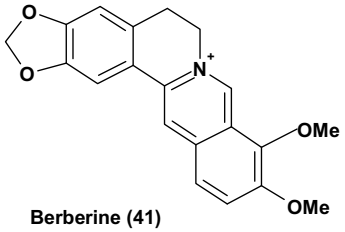
Calebin-A (38)



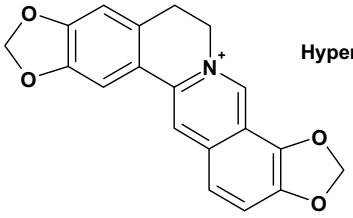
Huperzine A (39)



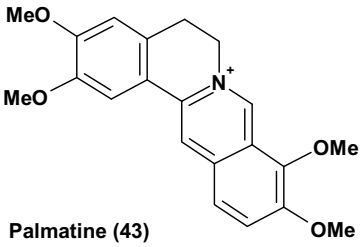
Hyperforin (40)



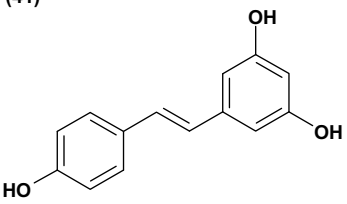
Berberine (41)



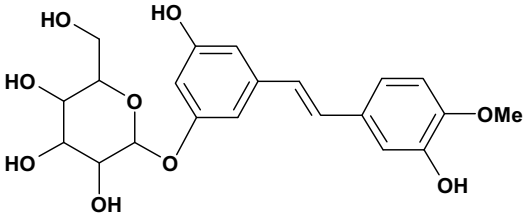
Coptisine (42)



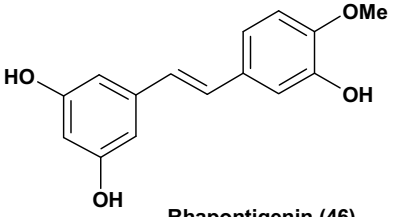
Palmatine (43)



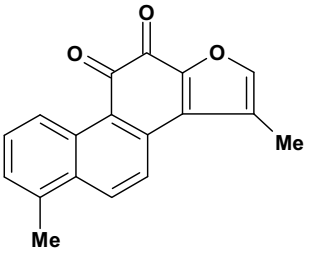
Resveratrol (44)



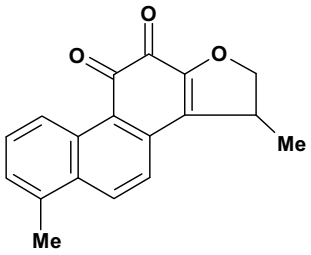
Rhaponticin (45)



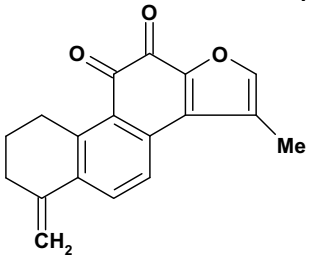
Rhapontigenin (46)



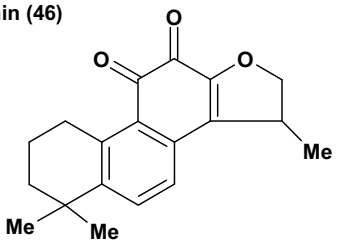
Tanshinone I (47)



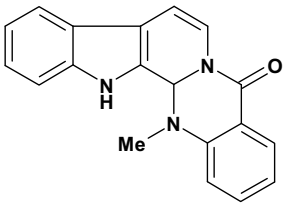
Dihydrotanshinone (48)



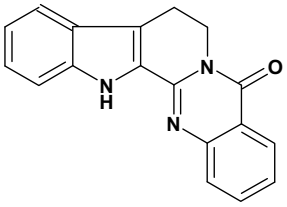
Methylene tanshiquinone (49)



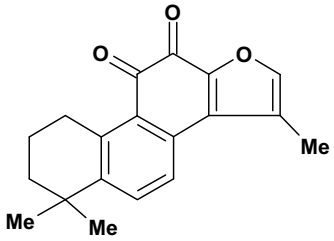
Cryptotanshinone (50)



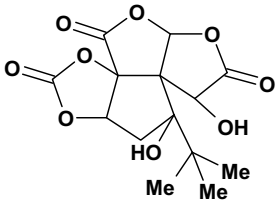
Dehydroevodiamine (52)



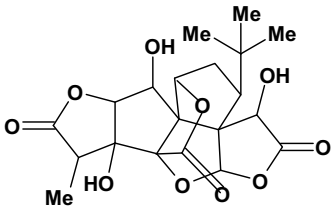
Rutaecarpine (53)



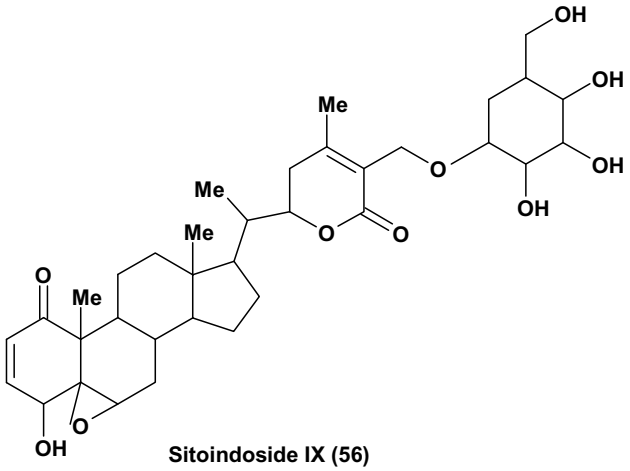
Tanshinone IIA (51)



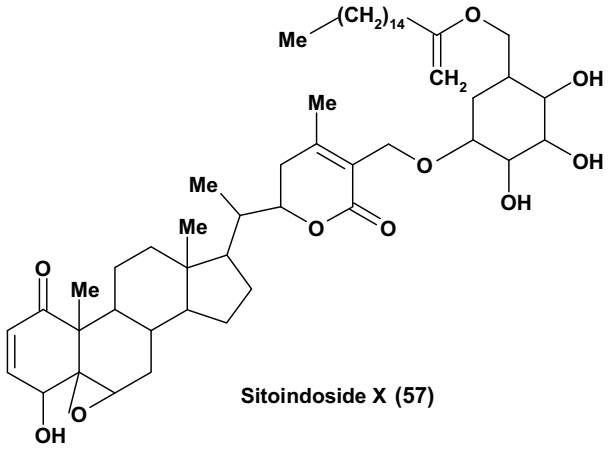
Bilobalide (54)



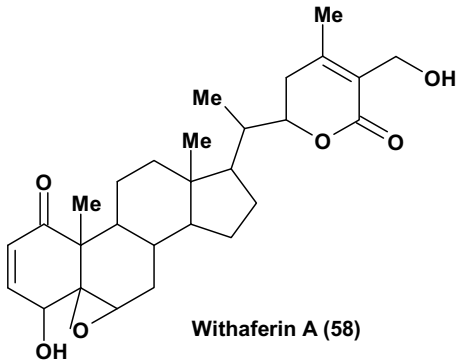
Ginkgolide B (55)



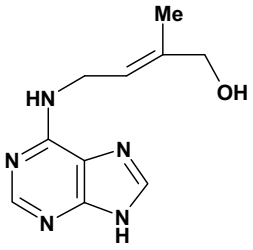
Sitoindoside IX (56)



Sitoindoside X (57)



Withaferin A (58)



Zeatin (59)