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Review

Medicinal plants with cholinesterase inhibitory activity: A Review

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Alzheimer's disease (AD), a common neurodegenerative disease, is characterized by low levels in the brain of the neurotransmitter, acetylcholine (ACh). Clinical treatment of this disease is palliative and relies mostly on enhancing cholinergic function by stimulation of cholinergic receptors or prolonging the availability of ACh released into the neuronal synaptic cleft by use of agents which restore or improve the levels of acetylcholine. Inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), enzymes which breakdown acetylcholine, are considered as a promising strategy for the treatment of AD. A potential source of AChE and BChE inhibitors is provided by the abundance of plants in nature, and natural products continue to provide useful drugs and templates for the development of other compounds. The present work constitutes a review of the literature on 123 species of medicinal plants that have been tested for AChE inhibitory activity and 42 plant species which have been tested for BChE inhibitory activity. The plant species listed are potential cholinesterase inhibitors and may aid researchers in their study of natural products which may be useful in the treatment of AD.

Key words: Alzheimer's disease, acetylcholine, acetylcholinesterase, butyrylcholinesterase and medicinal plants.

INTRODUCTION

Neurodegenerative disease is a term applied to a variety of conditions arising from a chronic breakdown and deterioration of the neurons, particularly those of the central nervous system (Houghton and Howes, 2005). Alzheimer's disease (AD) was first described in 1906 by a Bavarian neuropsychiatrist Alois Alzheimer (Hostettmann et al., 2006). It is a complex, multifactoral, progressive, neurodegenerative disease primarily affecting the elderly population and is estimated to account for 50 - 60% of dementia cases in persons over 65 years of age (Frank and Gupta, 2005). The pathological features identified in the central nervous system (CNS) in AD are amyloid plaques, neurofibrillary tangles, inflammatory processes and disturbance of neurotransmitters (Selkoe, 2001; Bossy-Wetzel et al., 2004). There is also a progressive loss of neurons in the basal forebrain, which is the major source of cholinergic innervations of the neocortex and hippocampus. These changes involve progressive and irreversible impairment of cognitive function, resulting mainly in a loss of memory, with neurological and neuropsychiatric disorders (Hostettmann et al., 2006).

The pathophysiology of AD is complex and involves several different biochemical pathways. The first neurotransmitter defect discovered in AD involved acetylcholine (ACh), which plays an important role in memory and learning. In the CNS, ACh stimulation of the nicotinic receptors appears to be associated with cognitive

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Abbreviations: AD, Alzheimer's disease; **CNS,** central nervous system; **ACh,** acetylcholine; **AChE,** acetylcholinesterase; **BChE,** butyrylcholinesterase; **DTNB,** 5,5´-bisdithionitrobenzoic acid; **ATCI,** acetylthiocholine iodide; **BTCCI,** butyrylthiocholine chloride; **TLC,** thin layer chromatography; **DPPH,** diphenyl picryl hydrazine; **XO,** xanthine oxidase; **EtOAc,** ethylacetate; **BHA,** butylated hydroxyanisole; **OSI,** oxidative stability instrument; **BHT,** butylated hydroxytoluene.

function. Normally, ACh is stored in the nerve terminals, in structures called vesicles and is released from the nerve endings when the nerve terminal is depolarized, thereby entering the synapse and binding to the receptor (Houghton et al., 2006). However, in patients with AD, the ACh which is released has a very short half-life due to the presence of large amounts of the enzymes; acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), which are both present in the brain and are detected among neurofibrillary tangles and neuritic plaques (Beard et al., 1995; Orhan et al., 2004). These enzymes hydrolyse the ester bond in the ACh molecule, leading to loss of stimulatory activity.

The increase in life expectancy during the 20th century has concomitantly increased the number of people suffering from the disease. There are considerable financial, social and emotional burdens associated with the caring for patients with this disease (Akhondzadeh and Noroozian, 2002). In fact, in advanced industrialized and post-industrialized societies, where life expectancy is long, this disease is a major cause of morbidity and it imposes severe strains on the social welfare systems. It is estimated that in the USA, at least 5 million people are affected by AD (Houghton and Howes, 2005).

Approaches to enhance cholinergic function in AD have included stimulation of cholinergic receptors or prolonging the availability of ACh released into the neuronal synaptic cleft by use of agents which restore the level of acetylcholine through inhibition of both AChE and BChE. BChE, primarily associated with glial cells and specific neuronal pathways cleaves ACh in a similar manner to AChE to terminate its physiological action. Such studies, together with a statistically slower decline in the cognitive performance of dementia patients possessing specific BChE polymorphisms that naturally lower BChE activity, have targeted BChE as a new approach to intercede in the progression of AD (Loizzo et al., 2009). Recently, Hodges (2006) demonstrated that the inhibition of AChE holds a key role not only to enhance cholinergic transmission in the brain but also to reduce the aggregation of β-amyloid and the formation of the neurotoxic fibrils in AD. Therefore, AChE and BChE inhibitors have become remarkable alternatives in treatment of AD (Orhan et al., 2004). Existing anticholinesterase drugs (example, tacrine, donepezil, physostigmine, galantamine and heptylphysostigmine) for the treatment of dementia are reported to have several dangerous adverse effects such as hepatotoxicity, short duration of biological action, low bioavailability, adverse cholinergic side effects in the periphery and a narrow therapeutic window (Hung et al., 2008; Sancheti et al., 2009).

The history of drug discovery has shown that plants contain active compounds that have become new sources to investigate for the pharmaceutical industry. Plant constituents may not only act synergistically with other constituents from the same plant but may also enhance the activity of compounds or counteract toxic effects of compounds from other plant species (Howes and Houghton, 2003). In traditional practices, numerous plants have been used to treat cognitive disorders, including neurodegenerative diseases and different neuropharmacological disorders (Mukherjee et al., 2007a). Yokukansan, a Chinese herbal remedy which is used to treat various neurological states has been reported as being effective with no adverse effects (De Caires and Steenkamp, 2010). Also, galanthamine, an alkaloid from snowdrop, has been approved by the Food and Drug Administration in the United States for use in the treatment of Alzheimer's disease (Ingkaninan et al., 2003; Heinrich and Teoh, 2004). Since AD has become a public health burden, and the commonly available synthetic drugs have undesirable side-effects, new treatment strategies based on medicinal plants have been the subject of current focus. This article summarizes the plants so far reported to have AChE and BChE inhibitory activity.

EXPERIMENTAL APPROACHES

The colorimetric method of Ellman et al. (1961) which is based on determining the amount of thiocholine released when acetylthiocholine or butyrylthiocholine is hydrolysed by AChE or BChE is widely used. The thiocholine released is quantified by its reaction with 5,5´-bisdithionitrobenzoic acid (DTNB), which produces a yellow 5-thio-2-nitrobenzoate anion. Several 96-well microplate assays have been derived from Ellman's method with some modifications which have enabled determinations to be performed with a much higher throughput (Houghton et al., 2006).

The Ellman reaction for detecting AChE and BChE inhibitory activity has also been adapted for thin layer chromatography (TLC) plates. Samples are spotted on the plate before standard development, after which a solution of DTNB and acetylthiocholine iodide (ATCI) or butyrylthiocholine chloride (BTCCl) is sprayed until the plate is saturated. Thereafter the enzyme solution is sprayed on the plate and it is incubated for 5 min. A yellow coloration with white spots is indicative of inhibitory activity. This provides an extremely rapid method to screen large numbers of samples to discover new inhibitors of AChE and BChE (Hostettmann et al., 2006). However, this method is known to give a number of false-positive effects. To rule out such results, plates are first sprayed with DTNB, followed by a mixture of the enzyme and ATCI where the occurrence of white spots is indicative of false positive results (Adsersen et al., 2006; Houghton et al., 2006). A similar method for TLC detection has been introduced which uses acetylnaphthol as the substrate and measures the amount of naphthol, the reaction product formed, by its chromogenic reaction with Fast Blue B salt (Giovanni et al., 2008).

Other methods and assays used for detection and

quantification of AChE and BChE inhibition include high performance liquid chromatography (HPLC) with on-line coupled UV-MS-biochemical detection (Ingkaninan et al., 2000), fluorometry, radiometric assay, mass spectrometry, and assays based on immobilized enzyme (Hostettmann et al., 2006). Fluorometric methods are reported to be more sensitive than colorimetric methods for the assay of AChE and BChE. Fluorogenic substrates such as 2-naphthyl acetate, indoxyl acetate, resorufin butyrate and fluorofore coumarinylphenylmaleimide have been utilized (Rhee et al., 2003). A limitation of the flow assay could be that the presence in the plant extract of fluorescent compounds with similar excitation and emission wavelengths as the product of the enzyme reaction results in a positive peak which might obscure inhibitory activity.

CHOLINESTERASE INHIBITORY ACTIVITY OF PLANT EXTRACTS

Acetylcholinesterase inhibitory activity

Extracts of several medicinal plants have been reported to show AChE inhibitory activity. A summary of screening studies of these plants is provided in Table 1 in alphabetical order of their family, together with their scientific names, plant part, solvent extract, percentage inhibition and concentration at which the enzyme is inhibited.

Aqueous and methanol extracts of 11 plants, used in Danish folk medicine for improvement of memory and cognition, and three *Corydalis* species have been tested for their AChE inhibitory activity (Adsersen et al., 2006). The authors reported significant dose-dependent inhibitory activity for extracts of the *Corydalis* species whereas only moderate inhibition of the enzyme was observed for extracts of *Ruta graveolens* L., *Lavandula augustifolia* Miller, *Rosmarinus officinalis* L., *Petroselinum crispum* (Mil.) Nym. ex A. W. Hill., and *Mentha spicata* L. The latter five species contain essential oils with terpenes, a group of compounds reported to have AChE inhibitory activity (Perry et al., 2000; Adsersen et al., 2006).

Ferreira et al. (2006) reported the AChE inhibitory activity of the essential oil, ethanol extract and decoction of ten plant species from Portugal. Among the plant extracts screened, *Melissa officinalis*, *Paronychia argentea*, *Sanguisorba minor*, *Hypericum undulatum* and *Malva silvestris* are used in herbal medicine, *Laurus nobilis* and *Mentha suaveolens* as condiments, and *Lavandula augustifolia* and *Lavandula pedunculata* as aromatics. *M. officinalis* and *M. suaveolens* showed AChE inhibitory capacity higher than 50% in the essential oil fraction. The ethanol extract of *L. nobilis*, *H. undulatum* and *S. minor* exhibited AChE inhibition of 64% (1 mg/ml), 68% (0.5 mg/ml) and 78% (1 mg/ml), respectively. In addition decoctions of *L. pedunculata*, *M. suaveolens* and *H. undulatum* at 5 mg/ml, exhibited percentage inhibitions of 68, 69 and 82%, respectively.

Mukherjee et al. (2007b) reported the AChE inhibitory activity of the hydroalcohol extracts of six herbs used in Indian system of medicine. The hydroalcohol extract from *Centella asiatica, Nardostachys jatamansi, Myristica fragrans, Evalvulus alsinoides* inhibited 50% of AChE activity (IC_{50}) at concentrations of 100 - 150 µg/ml. The AChE inhibitory activity of petroleum ether, chloroform, ethyl acetate and methanol extracts obtained from 14 *Salvia* species growing in Turkey has been reported (Orhan et al., 2007). Most of the extracts did not show any activity against AChE at 0.2 mg/ml. The most active extracts at 1 mg/ml for AChE inhibition were the petroleum ether extract of *S. albimaculata* (89.4%) and chloroform extract of *S. cyanescens* (80.2%). In a recent study by Khadri et al. (2010), the aqueous extract, proanthocyanidin rich extract and organic extracts of *Cymbopogon schoenanthus* shoots from South Tunisia all showed good AChE inhibitory activity.

Butyrylcholinesterase inhibitory activity

BChE has been shown to be implicated in the progression of AD as it also reduces the availability of ACh which is an important neurotransmitter in AD. A summary of medicinal plants which have been screened and reported to have BChE inhibitory activity are listed in Table 1.

The chloroform: methanol (1:1) extracts of 21 plant species were screened for their anticholinesterase activity on BChE enzyme by the *in vitro* method of Ellman (Orhan et al., 2004). The extracts did not show any noticeable inhibitory activity against the enzyme at 10 µg/ml, however, extracts of *Rhododendron ponticum* subsp. *ponticum*, *Corydalis solida* subsp. *solida* and *Buxus semperivirens* showed inhibition at 1 mg/ml. Loizzo et al. (2009) evaluated the essential oils of *Origanum ehrenbergii* and *Origanum syriacum* both collected from Lebanon for their BChE inhibitory activity when using a modification of Ellman's method, with *O. ehrenbergii* showing the highest activity. The data obtained from this and other studies on both oils showed that they could be used as a valuable new flavor with functional properties for food or nutriceutical products with particular relevance to supplements for the elderly.

Petroleum ether, chloroform, ethyl acetate and methanol extracts of 14 *Salvia* species have also been screened for possible BChE inhibitory activity. At 1 mg/ml, the ethyl acetate extracts of *Salvia frigida* and *Salvia migrostegia*, chloroform extracts of *Salvia candidissima* ssp. *occidentalis* and *Salvia ceratophylla*, as well as petroleum ether extract of *Salvia cyanescens* inhibit BChE by more than 90% (Orhan et al., 2007).

DISCUSSION

Inhibition of AChE, the key enzyme in the breakdown of

Table 1. Medicinal Plants with cholinesterase inhibitory activity

Family and botanical name	Parts used	Type of extract (solvent)	AChE Method; Activity (% inhibition) (concentration of plant extract tested)	BChE Method; Activity (% inhibition) (concentration of plant extract tested)	References
Acanthaceae					
Acanthus ebracteatus Vahl.	Aerial part	Methanol	TLC and 96 well plate; 36.19 ± 8.00 (0.1mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007a)
Andrographis paniculata Nees.	Aerial part	Hydroalcohol	96 well plate; 50% (222.41µg/ml)*	ND	Mukherjee et al. (2007b)
Anacardiaceae					
Magnifera indica L.	Bark	Methanol	TLC and 96 well plate; 8.15 ± 0.77 (100 µg/ml)	ND	Vinutha et al. (2007)
	Bark	Water	TLC and 96 well plate; 6.29 ± 0.37 (100µg/ml)	ND	Vinutha et al. (2007)
Semecarpus anacardium Linn. f.	Bark	Methanol	TLC and 96 well plate; 69.94 ± 0.75 (100 µg/ml)	ND	Vinutha et al. (2007)
	Bark	Water	TLC and 96 well plate; 1.09 ± 0.37 (100 µg/ml)	ND	Vinutha et al. (2007)
Apiaceae					
Carum carvi L.	Radix	Methanol	TLC and 96 well plate; 11.00 ± 0.00 (0.1mg/ml)	ND	Adsersen et al. (2006)
Petroselinum crispum (Mil.) Nym. ex A. W. Hill.	Radix	Methanol	TLC and 96 well plate; 21.00 ± 0.00 (0.1mg/ml)	ND	Adsersen et al. (2006)
Pimpinella anisum L.	Fructus	Methanol	TLC and 96 well plate; 3.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
Apocynaceae					
Tabernaemontana divaricata L.	Roots	Ethanol	96 well plate; 50% (2.56 mg/l)*	96 well plate; 50% (76.95 mg/l)*	Chattipakorn et al. (2007)
Araceae					
Acorus calamus L.	Rhizomes	Methanol	96 well plate; 50% (791.35µg/ml)*	ND	Ahmed et al. (2009)
Asteraceae					
Carthamus tinctorius L.	Flower	Methanol	TLC and 96 well plate; 30.33 ± 9.22 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Brassicaceae					
Capsella bursa-pastoris (L.) Medik.	Whole plant	Methanol	96 well plate; 10.00 ± 2.00 (5 mg/ml)	96 well plate; 13.00 ± 1.00 (5 mg/ml)	Sancheti et al. (2009)

Table 1. Cont'd

Buxaceae					
Buxus sempervirens L.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 61.76 ± 0.76 (1 mg/ml)	ND	Orhan et al. (2004); Mukherjee et al. (2007 a)
Caesalpinaceae					
Robinia pseudoacacia L.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 26.32 ± 0.82 (1 mg/ml)	96 well plate; 31.47 ± 0.99 (1mg/ml)	Orhan et al. (2004)
Caryophyllaceae					
Paronychia argentea Lam.	Aerial parts	Water	UV spectophotometry; 26.10 ± 1.20 (5 mg/ml)	ND	Ferreira et al. (2006)
	Aerial parts	Essential oil	UV spectophotometry; 49.50 ± 1.00 (1 mg/ml)	ND	Ferreira et al. (2006)
	Aerial parts	Ethanol	UV spectophotometry; 48.70 ± 6.10 (0.5 mg/ml)	ND	Ferreira et al. (2006)
Celastraceae					
Euonymus sachalinensis (F. Schmidt.) Maxim.	Leaf	Methanol	96 well plate; 10.00 ± 3.00 (5 mg/ml)	96 well plate; 43.00 ± 1.00 (5 mg/ml)	Sancheti et al. (2009)
Combretaceae					
Combretum kraussii Hochst.	Leaf	Ethyl acetate	TLC and 96 well plate; 96.00 ± 4.60 (1 mg/ml)	ND	Eldeen et al. (2005)
	Leaf	Ethanol	TLC and 96 well plate; 88.00 ± 3.10 (1 mg/ml)	ND	Eldeen et al. (2005)
	Bark	Ethyl acetate	TLC and 96 well plate; 82.00 ± 6.10 (1 mg/ml)	ND	Eldeen et al. (2005)
	Bark	Ethanol	TLC and 96 well plate; 83.00 ± 4.50(1 mg/ml)	ND	Eldeen et al. (2005)
	Root	Ethyl acetate	TLC and 96 well plate; 81.00 ± 4.10 (1 mg/ml)	ND	Eldeen et al. (2005)
	Root	Ethanol	TLC and 96 well plate; 82.00 ± 5.20 (1 mg/ml)	ND	Eldeen et al. (2005)
Terminalia bellirica (Gaertn.) Roxb.	Fruit	Methanol	TLC and 96 well plate; 39.68 ± 8.15 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007a)
Terminalia chebula Retz.	Fruit	Methanol	96 well plate; 89.00 ± 1.00 (5 mg/ml)	96 well plate; 95.00 ± 1.00 (5 mg/ml)	Sancheti et al. (2009)
Convolvulaceae					
Convolvulus pluricaulis Choisy.	Whole plant	Methanol	TLC and 96 well plate; 2.22 ± 1.17 (100 µg/ml)	ND	Vinutha et al. (2007)
Evalvulus alsinoides L.	Whole plant	Hydro alcohol	96 well plate; 50% (141.76 µg/ml)*	ND	Mukherjee et al. (2007 b)

Table 1. Cont'd

Crassulaceae					
Rhodiola rosea L.	Root	Methanol	96 well plate; 42.00 ± 3.20 (10 g/l)	ND	Hillhouse et al. (2004); Mukherjee et al. (2007 a)
Cupressaceae					
Chamaecyparis pisifera (Siebold and Zuccarini) Endlicher	Whole plant	Methanol	96 well plate; 59.00 ± 2.00 (5 mg/ml)	96 well plate; 62.00 ± 2.00 (5 mg/ml)	Sancheti et al. (2009)
Cyperaceae					
Cyperus rotundus L.	Whole plant	Methanol	TLC and 96 well plate; 44.19 ± 2.27 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Dioscoreaceae					
Dioscorea bulbifera L.	Whole plant	Methanol	96 well plate; 79.00 ± 2.00 (5 mg/ml)	96 well plate; 82.00 ± 2.00 (5 mg/ml)	Sancheti et al. (2009)
Ericaceae					
Rhododendron luteum Sweet.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 76.32 ± 0.58 (1 mg/ml)	96 well plate; 69.14 ± 1.89 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Rhododendron ponticum L. subsp. *Ponticum*	Whole plant	Chloroform: methanol (1:1)	96 well plate; 93.03 ± 1.12 (1 mg/ml)	96 well plate; 95.23 ± 1.28 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Rhododendron schlippenbachii Maxim.	Whole plant	Methanol	96 well plate; 67.00 ± 1.00 (5 mg/ml)	96 well plate; 63.00 ± 2.00 (5 mg/ml)	Sancheti et al. (2009)
Euphorbiaceae					
Euphorbia antiquorum L.	Stem	Methanol	TLC and 96 well plate; 42.31 ± 9.10 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Fabaceae					
Albizia adianthifolia (Schumach.) W.F. Wight.	Bark	Ethyl acetate	TLC and 96 well plate; 61.00 ± 5.10 (1 mg/ml)	ND	Eldeen et al. (2005)
	Bark	Ethanol	TLC and 96 well plate; 53.00 ± 2.20 (1 mg/ml)	ND	Eldeen et al. (2005)
	Root	Ethyl acetate	TLC and 96 well plate; 45.00 ± 2.10 (1 mg/ml)	ND	Eldeen et al. (2005)
	Root	Ethanol	TLC and 96 well plate; 51.00 ± 3.40 (1 mg/ml)	ND	Eldeen et al. (2005)
Vicia faba L.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 45.23 ± 1.03 (1 mg/ml)	96 well plate; 55.85 ± 0.48 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)

Table 1. Cont'd

Fumariaceae					
Fumaria asepala Boiss.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 91.99 ± 0.70 (1 mg/ml)	96 well plate; 93.12 ± 0.28 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Fumaria capreolata L.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 96.89 ± 0.17 (1 mg/ml)	96 well plate; 89.24 ± 0.83 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Fumaria cilicica Hausskn.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 88.03 ± 0.65 (1 mg/ml)	96 well plate; 80.03 ± 0.28 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Fumaria densiflora DC.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 93.42 ± 0.92 (1 mg/ml)	96 well plate; 85.66 ± 1.24 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Fumaria flabellata L.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 92.14 ± 1.01 (1 mg/ml)	96 well plate; 87.91 ± 0.61 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Fumaria judaica Boiss.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 96.47 ± 0.63 (1 mg/ml)	96 well plate; 98.43 ± 0.39 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Fumaria kralikii Jordan	Whole plant	Chloroform: methanol (1:1)	96 well plate; 84.98 ± 1.07 (1 mg/ml)	96 well plate; 75.43 ± 0.98 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Fumaria macrocarpa Boiss. ex Hausskn.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 93.43 ± 0.64 (1 mg/ml)	96 well plate; 88.74 ± 0.34 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Fumaria parviflora Lam.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 87.02 ± 0.31 (1 mg/ml)	96 well plate; 87.09 ± 1.45 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Fumaria petteri Reichb subsp. *thuretii* (Boiss.)	Whole plant	Chloroform: methanol (1:1)	96 well plate; 89.45 ± 0.86 (1 mg/ml)	96 well plate; 87.32 ± 0.76 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Fumaria vaillantii Lois.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 94.23 ± 0.47 (1 mg/ml)	96 well plate; 99.32 ± 0.25 (1 mg/ml)	Orhan et al. (2004); Mukherjee et al. (2007 a)
Ginkgoaceae					
Ginkgo biloba L.	Whole plant	Ethanol	96 well plate; 50% (268.33 µg)*	ND	Perry et al. (1998); Das et al. (2002); Mukherjee et al. (2007 a)
Guttiferae					
Mammea harmandii Kosterm.	Flower	Methanol	TLC and 96 well plate; 33.63 ± 8.00 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Hypericaceae					
Hypericum undulatum Shoubs. ex Willd.	Flower	Water	UV spectophotometry; 81.70 ± 3.40 (5 mg/ml)	ND	Ferreira et al. (2006)
	Flower	Essential oil	UV spectophotometry; 30.30 ± 19.70 (1 mg/ml)	ND	Ferreira et al. (2006)
	Flower	Ethanol	UV spectophotometry; 68.40 ± 4.70 (0.5 mg/ml)	ND	Ferreira et al. (2006)

Table 1. Cont'd

Lamiaceae					
Lavandula augustifolia Miller	Whole plant	Methanol	TLC and 96 well plate; 34.00 ± 0.00 (0.1 mg/ml)	ND	Ferreira et al. (2006)
	Aerial parts	Essential oil	UV spectophotometry; 39.50 ± 8.60 (1 mg/ml)	ND	Ferreira et al. (2006)
	Aerial parts	Ethanol	UV spectophotometry; 64.30 ± 9.00 (1 mg/ml)	ND	Ferreira et al. (2006)
Lavandula pedunculata (Miller) Cav.	Aerial parts	Water	UV spectophotometry; 67.80 ± 10.70 (5 mg/ml)	ND	Ferreira et al. (2006)
	Aerial parts	Essential oil	UV spectophotometry; 56.50 ± 4.90 (0.5 mg/ml)	ND	Ferreira et al. (2006)
	Aerial parts	Ethanol	UV spectophotometry; 42.00 ± 16.80 (1 mg/ml)	ND	Ferreira et al. (2006)
Mentha spicata L.	Whole plant	Methanol	TLC and 96 well plate; 15.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006) Ferreira et al. (2006)
Mentha suaveolens Ehrh.	Aerial parts	Water	UV spectophotometry; 68.90 ± 2.50 (5 mg/ml)	ND	
	Aerial parts	Essential oil	UV spectophotometry; 52.40 ± 2.50 (1 mg/ml)	ND	Ferreira et al. (2006)
	Aerial parts	Ethanol	UV spectophotometry; 27.10 ± 2.70 (1 mg/ml)	ND	Ferreira et al. (2006)
Origanum vulgare L.	Whole plant	Methanol	TLC and 96 well plate; 3.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
Origanum ehrenbergii Boiss	Aerial parts	Essential oil	UV spectophotometry; 50% (0.3 µg/ml)*	UV spectophotometry; 50% (0.3 µg/ml)*	Loizzo et al. (2009)
Origanum syriacum L.	Aerial parts	Essential oil	UV spectophotometry; 50% (1.7 µg/ml)*	UV spectophotometry; 50% (1.6 µg/ml)*	Loizzo et al. (2009)
Rosmarinus officinalis L.	Whole plant	Methanol	TLC and 96 well plate; 17.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
Salvia albimaculata Hedge and Hub	Whole plant	Petroleum ether	96 well plate; 89.40 ± 2.07 (1 mg/ml)	96 well plate; 73.90 ± 0.76 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Chloroform	NI	96 well plate; 87.90 ± 0.22 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 51.70 ± 3.22 (1 mg/ml)	96 well plate; 69.80 ± 1.99 (1 mg/ml)	Orhan et al. (2007)

Table 1. Cont'd

	Whole plant	Methanol	96 well plate; 38.90 ± 3.22 (1 mg/ml)	96 well plate; 27.40 ± 1.32 (1 mg/ml)	Orhan et al. (2007)
Salvia aucheri Bentham var. *canescens* Boiss and Heldr	Whole plant	Chloroform	96 well plate; 64.50 ± 1.03 (1 mg/ml)	96 well plate; 77.60 ± 3.76 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 53.40 ± 1.59 (1 mg/ml)	96 well plate; 69.60 ± 2.15 (1mg/ml)	Orhan et al. (2007)
	Whole plant	Methanol	96 well plate; 39.90 ± 1.17 (1 mg/ml)	96 well plate; 12.60 ± 1.05 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 27.30 ± 0.98 (1 mg/ml)	96 well plate; 59.90 ± 378.00 (1 mg/ml)	Orhan et al. (2007)
Salvia candidissima Vahl. *ssp. occidentalis*	Whole plant	Chloroform	96 well plate; 48.60 ± 5.13 (1 mg/ml)	96 well plate; 91.10 ± 1.98 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 46.10 ± 1.28 (1 mg/ml)	96 well plate; 77.80 ± 0.93 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 39.40 ± 4.31 (1 mg/ml)	96 well plate; 55.60 ± 0.28 (1 mg/ml)	Orhan et al. (2007)
Salvia ceratophylla L.	Whole plant	Chloroform	96 well plate; 30.80 ± 5.25 (1 mg/ml)	96 well plate; 91.10 ± 1.98 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 19.30 ± 1.57 (1 mg/ml)	96 well plate; 29.20 ± 0.77 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Methanol	96 well plate; 27.80 ± 2.82 (1 mg/ml)	96 well plate; 34.90 ± 6.50 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	NI	96 well plate; 38.80 ± 4.94 (1 mg/ml)	Orhan et al. (2007)
Salvia cryptantha Montbret and Bentham	Whole plant	Chloroform	96 well plate; 24.90 ± 1.65 (1 mg/ml)	NI	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 73.30 ± 2.55 (1 mg/ml)	96 well plate; 53.60 ± 0.67 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Methanol	96 well plate; 47.20 ± 5.18 (1 mg/ml)	96 well plate; 36.30 ± 2.79 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 71.80 ± 2.62 (1 mg/ml)	96 well plate; 92.00 ± 0.41 (1mg/ml)	Orhan et al. (2007)

Table 1. Cont'd

Salvia cyanescens Boiss and Bal.	Whole plant	Chloroform	96 well plate; 80.20 ± 4.35 (1 mg/ml)	96 well plate; 91.80 ± 0.54 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 51.20 ± 3.78 (1 mg/ml)	96 well plate; 56.90 ± 1.03 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Methanol	96 well plate; 9.00 ± 0.88 (1 mg/ml)	96 well plate; 13.10 ± 0.70 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 37.70 ± 5.35 (1 mg/ml)	96 well plate; 67.40 ± 3.59 (1 mg/ml)	Orhan et al. (2007)
Salvia forskahlei L.	Whole plant	Chloroform	96 well plate; 41.30 ± 2.91 (1 mg/ml)	96 well plate; 60.20 ± 4.42 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 47.00 ± 2.31 (1 mg/ml)	96 well plate; 62.90 ± 0.67 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Methanol	96 well plate; 35.80 ± 2.46 (1 mg/ml)	96 well plate; 46.70 ± 3.69 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 25.20 ± 4.46 (1 mg/ml)	96 well plate; 69.30 ± 1.65 (1mg/ml)	Orhan et al. (2007)
Salvia frigida Boiss	Whole plant	Chloroform	96 well plate; 53.70 ± 2.25 (1 mg/ml)	96 well plate; 77.80 ± 0.21 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 59.50 ± 0.45 (1 mg/ml)	96 well plate; 92.20 ± 0.29 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Methanol	96 well plate; 32.60 ± 0.01 (1 mg/ml)	96 well plate; 59.90 ± 2.30 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 6.20 ± 0.24 (1 mg/ml)	96 well plate; 54.90 ± 1.95 (1 mg/ml)	Orhan et al. (2007)
Salvia halophila Hedge	Whole plant	Chloroform	NI	96 well plate; 53.90 ± 2.16 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 36.10 ± 1.21 (1 mg/ml)	96 well plate; 37.20 ± 3.88 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 18.90 ± 1.21 (1 mg/ml)	96 well plate; 50.90 ± 4.20 (1 mg/ml)	Orhan et al. (2007)
Salvia lavandulaefolia Vahl.	Whole plant	Steam distilled oil	96 well plate; 63.00 ± 3.70 (0.1 µg/ml)	ND	Perry et al. (1996, 2000, 2001); Mukherjee et al. (2007 a)
Salvia migrostegia Boiss and Bal.	Whole plant	Chloroform	96 well plate; 36.40 ± 5.45 (1 mg/ml)	96 well plate; 62.50 ± 1.31 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 37.10 ± 3.15 (1 mg/ml)	96 well plate; 89.60 ± 0.67 (1 mg/ml)	Orhan et al. (2007)

Table 1. Cont'd

	Whole plant	Methanol	96 well plate; 23.60 ± 0.61 (1 mg/ml)	96 well plate; 32.60 ± 3.40 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	NI	96 well plate; 22.10 ± 2.70 (1 mg/ml)	Orhan et al. (2007)
Salvia multicaulis Vahl.	Whole plant	Ethyl acetate	NI	96 well plate; 64.30 ± 1.02 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Methanol	96 well plate; 47.70 ± 3.58 (1 mg/ml)	96 well plate; 36.20 ± 0.93 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 21.40 ± 3.91 (1 mg/ml)	96 well plate; 68.80 ± 3.80 (1 mg/ml)	Orhan et al. (2007)
Salvia officinalis L.	Whole plant	Ethanol	96 well plate; 68.20 ± 15.60 (2.5 mg/ml)	ND	Perry et al. (1996, 2000, 2001); Mukherjee et al. (2007 a)
	Whole plant	Steam distilled oil	96 well plate; 52.40 ± 0.80 (0.1 µg/ml)	ND	Perry et al. (1996, 2000, 2001); Mukherjee et al. (2007 a)
Salvia sclarea L.	Whole plant	Chloroform	96 well plate; 55.30 ± 0.98 (1 mg/ml)	96 well plate; 59.90 ± 0.50 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 33.50 ± 4.94 (1 mg/ml)	96 well plate; 75.70 ± 1.83 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Methanol	96 well plate; 25.30 ± 1.86 (1 mg/ml)	96 well plate; 15.10 ± 1.76 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 25.80 ± 4.51 (1 mg/ml)	96 well plate; 52.60 ± 2.92 (1 mg/ml)	Orhan et al. (2007)
Salvia syriaca L.	Whole plant	Chloroform	96 well plate; 66.90 ± 2.49 (1 mg/ml)	96 well plate; 87.30 ± 1.99 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	96 well plate; 49.80 ± 2.41 (1 mg/ml)	96 well plate; 70.90 ± 2.69 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Methanol	96 well plate; 12.10 ± 1.22 (1 mg/ml)	96 well plate; 12.30 ± 1.10 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 33.40 ± 2.98 (1 mg/ml)	96 well plate; 63.50 ± 2.12 (1 mg/ml)	Orhan et al. (2007)
Salvia triloba L.	Aerial parts	Ethanol	96 well plate; 54.30 ± 3.20 (2 mg/ml)	ND	Orhan et al. (2007)
Salvia verticillata L. ssp. *amasiaca*	Whole plant	Chloroform	NI	96 well plate; 55.70 ± 0.55 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Ethyl acetate	NI	96 well plate; 53.30 ± 5.50 (1 mg/ml)	Orhan et al. (2007)

Table 1. Cont'd

	Whole plant	Methanol	96 well plate; 39.10 ± 3.10 (1 mg/ml)	96 well plate; 72.00 ± 2.99 (1 mg/ml)	Orhan et al. (2007)
	Whole plant	Petroleum ether	96 well plate; 45.60 ± 4.17 (1 mg/ml)	96 well plate; 85.00 ± 53.10 (1 mg/ml)	Orhan et al. (2007)
Teucrium polium L.	Aerial parts	Ethanol	96 well plate; 65.80 ± 3.70 (2 mg/ml)	ND	Orhan et al. (2009)
Lauraceae					
Laurus nobilis L.	Leaf	Decoction	UV spectophotometry; 56.10 ± 5.50 (5 mg/ml)	ND	Ferreira et al. (2006)
	Leaf	Essential oil	UV spectophotometry; 51.30 ± 1.70 (0.5 mg/ml)	ND	Ferreira et al. (2006)
	Leaf	Ethanol	UV spectophotometry; 64.30 ± 9.00 (1 mg/ml)	ND	Ferreira et al. (2006)
Leguminosae					
Albizia procera (Roxb.) Benth.	Bark	Methanol	TLC and 96 well plate; 40.71 ± 0.46 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Butea superba Roxb.	Root barks	Methanol	TLC and 96 well plate; 55.87 ± 5.83 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Cassia fistula L.	Root	Methanol	TLC and 96 well plate; 54.13 ± 3.90 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Mimosa pudica L.	Whole plant	Water	TLC and 96 well plate; 1.68 ± 0.22 (100 µg/ml)	ND	Vinutha et al. (2007)
Trigonella foenum graecum L.	Seeds	Hydro alcohol	TLC and 96 well plate; 50% (140.26 µg)*	ND	SatheeshKumar et al. (2009)
	Seeds	Ethyl acetate	TLC and 96 well plate; 50% (53 µg)*	ND	SatheeshKumar et al. (2009)
	Seeds	Chloroform	TLC and 96 well plate; 50% (146.94 µg)*	ND	SatheeshKumar et al. (2009)
Lycopodiaceae					
Lycopodium clavatum L.	Whole plant	Chloroform: methanol (1:1)	96 well plate; 49.85 ± 1.33 (1 mg/ml)	ND	Orhan et al. (2004); Mukherjee et al. (2007 a)
Magnoliaceae					
Michelia champaca L.	Leaf	Methanol	TLC and 96 well plate; 34.88 ± 4.56 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Malvaceae					
Abutilon indicum L.	Whole plant	Methanol	TLC and 96 well plate; 30.66 ± 1.06 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)

Table 1. Cont'd

Malva silvestris L.	Aerial parts	Aqueous	UV spectophotometry; 25.00 ± 5.70 (5 mg/ml)	ND	Ferreira et al. (2006)
	Aerial parts	Essential oil	UV spectophotometry; 28.10 ± 2.90 (0.1 mg/ml)	ND	Ferreira et al. (2006)
Meliaceae					
Azadirachta indica A. juss.	Bark	Aqueous	TLC and 96 well plate; 5.89 ± 0.33 (100 µg/ml)	ND	Vinutha et al. (2007)
Trichilia dregeana Sond.	Bark	Ethyl acetate	TLC and 96 well plate; 55.00 ± 4.40 (1 mg/ml)	ND	Eldeen et al. (2005)
Menispermaceae					
Stephania suberosa Forman.	Roots	Methanol	TLC and 96 well plate; 91.93 ± 10.80 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Tiliacora triandra (Colebr.) Diel	Root	Methanol	TLC and 96 well plate; 42.29 ± 2.89 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Tinospora cordifolia Miers	Stem	Methanol	TLC and 96 well plate; 69.43 ± 0.37 (100 µg/ml)	ND	Vinutha et al. (2007)
	Stem	Aqueous	TLC and 96 well plate; 12.92 ± 0.26 (100 µg/ml)	ND	Vinutha et al. (2007)
Mimosaceae					
Acacia nilotica (L.) Willd. ex Del. spp. *kraussiana* (Benth.) Brenan	Leaf	Ethyl acetate	TLC and 96 well plate; 53.00 ± 3.70 (1 mg/ml)	ND	Eldeen et al. (2005)
	Leaf	Ethanol	TLC and 96 well plate; 56.00 ± 6.30 (1 mg/ml)	ND	Eldeen et al. (2005)
	Bark	Ethyl acetate	TLC and 96 well plate; 41.00 ± 2.10 (1 mg/ml)	ND	Eldeen et al. (2005)
Acacia sieberiana Dc. var. *woodii* (Burtt Davy) Keay & Brenan	Root	Ethyl acetate	TLC and 96 well plate; 60.00 ± 4.30 (1 mg/ml)	ND	Eldeen et al. (2005)
	Root	Ethanol	TLC and 96 well plate; 62.00 ± 4.1 (1 mg/ml)	ND	Eldeen et al. (2005)
Moraceae					
Ficus religiosa L.	Bark	Methanol	TLC and 96 well plate; 54.47 ± 1.28 (100 µg/ml)	ND	Vimutha et al. (2007)
Streblus asper Lour.	Seed	Methanol	TLC and 96 well plate; 30.51 ± 4.21 (0.1 µg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)

Table 1. Cont'd

Moringaceae					
Moringa oleifera Lam.	Bark	Methanol	TLC and 96 well plate; 4.99 ± 2.74 (100 µg/ml)	ND	Vinutha et al. (2007)
Musaceae					
Musa sapientum L.	Fruit	Methanol	TLC and 96 well plate; 29.14 ± 4.73 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Myristicaceae					
Myristica fragrans Houtt.	Seed	Hydroalcohol	96 well plate; 50% (133.28 µg/ml)*	ND	Mukherjee et al. (2007 b)
Myrsinaceae					
Embelia ribes Burm. f.	Fruit	Methanol	TLC and 96 well plate; 15.70 ± 1.19 (100 µg/ml)	ND	Vinutha et al. (2007)
	Root	Methanol	TLC and 96 well plate; 50.82 ± 0.71 (100 µg/ml)	ND	Vinutha et al. (2007)
Nelumbonaceae					
Nelumbo nucifera Gaertn.	Stamen	Methanol	TLC and 96 well plate; 23.77 ± 2.83 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Nyctaginaceae					
Boerhavia diffusa L.	Whole plant	Methanol	TLC and 96 well plate; 23.78 ± 1.17 (100 µg/ml)	ND	Vinutha et al. (2007)
Olacaceae					
Ptychopetalum olacoides Benth.	Root	Ethanol	Dose dependent activity at doses of 50 and 100 mg/kg, i.p.	ND	Siqueira et al. (2003); Mukherjee et al. (2007 a)
Papaveraceae					
Corydalis cava (L.) Schw. et K.	Whole plant	Water	TLC and 96 well plate; 62.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Whole plant	Methanol	TLC and 96 well plate; 85.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Tuber	Water	TLC and 96 well plate; 92.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Tuber	Methanol	TLC and 96 well plate; 92.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
Corydalis intermedia (L.) Mérat	Whole plant	Water	TLC and 96 well plate; 57.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Whole plant	Methanol	TLC and 96 well plate; 84.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)

Table 1. Cont'd

	Tuber	Water	TLC and 96 well plate; 78.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Tuber	Methanol	TLC and 96 well plate; 97.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
Corydalis solida (L.) Swartz ssp. *laxa*	Whole plant	Water	TLC and 96 well plate; 78.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Whole plant	Methanol	TLC and 96 well plate; 89.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Tuber	Water	TLC and 96 well plate; 85.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Tuber	Methanol	TLC and 96 well plate; 96.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
Corydalis solida (L.) Swartz ssp. slivenensis	Whole plant	Water	TLC and 96 well plate; 48.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Whole plant	Methanol	TLC and 96 well plate; 82.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Tuber	Water	TLC and 96 well plate; 87.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
	Tuber	Methanol	TLC and 96 well plate; 97.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al. (2006)
Piperaceae					
Piper interruptum Opiz	Stems	Methanol	TLC and 96 well plate; 65.16 ± 8.13 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Piper nigrum L.	Seeds	Methanol	TLC and 96 well plate; 58.02 ± 3.83 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Plumbaginaceae					
Plumbago indica L.	Root	Methanol	TLC and 96 well plate; 30.14 ± 3.28 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Poaceae					
Cymbopogon schoenanthus (L.) Spreng	Whole plant	Hexane	96 well plate; 50% (0.55 mg/ml)*	ND	Khadri et al. (2010)
	Whole plant	Dichloromethane	96 well plate; 50% (0.41 mg/ml)*	ND	Khadri et al. (2010)
	Whole plant	Ethyl acetate	96 well plate; 50% (0.35 mg/ml)*	ND	Khadri et al. (2010)
	Whole plant	Methanol	96 well plate; 50% (0.29 mg/ml)*	ND	Khadri et al. (2010)

Table 1. Cont'd

	Whole plant	Proanthocyanidin	96 well plate; 50% (0.75 mg/ml)*	ND	Khadri et al. (2010)
	Whole plant	Aqueous	96 well plate; 50% (0.42 mg/ml)*	ND	Khadri et al. (2010)
Pyrolaceae					
Pyrola japonica Klenze ex Alefeld	Whole plant	Methanol	96 well plate; 37.00 ± 2.00 (5 mg/ml)	96 well plate; 36.00 ± 3.00 (5 mg/ml)	Sancheti et al. (2009)
Rosaceae					
Sanguisorba minor Scop.	Aerial parts	Water	UV spectophotometry; 7.10 ± 1.60 (1 mg/ml)	ND	Ferreira et al. (2006)
	Aerial parts	Essential oil	UV spectophotometry; 46.10 ± 9.70 (1 mg/ml)	ND	Ferreira et al. (2006)
	Aerial parts	Ethanol	UV spectophotometry; 77.50 ± 2.20 (1 mg/ml)	ND	Ferreira et al. (2006)
Rubiaceae					
Paederia linearis Hook. f.	Whole plant	Methanol	TLC and 96 well plate; 29.31 ± 6.39 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Rubia cordifolia L.	Stem	Methanol	TLC and 96 well plate; 22.12 ± 2.22 (100 µg/ml)	ND	Vinutha et al. (2007)
	Stem	Aqueous	TLC and 96 well plate; 5.86 ± 0.37 (100 µg/ml)	ND	Vinutha et al. (2007)
Rutaceae					
Aegle marmelos (L.) Correa ex Roxb.	Fruit pulp	Methanol	TLC and 96 well plate; 44.65 ± 3.04 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Ruta graveolens L.	Whole plant	Water	TLC and 96 well plate; 22.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al.(2006)
	Whole plant	Methanol	TLC and 96 well plate; 39.00 ± 0.00 (0.1 mg/ml)	ND	Adsersen et al.(2006)
Sabiaceae					
Meliosma oldhamii Miq. ex. Maxim.	Whole plant	Methanol	96 well plate; 12.00 ± 2.00 (5 mg/ml)	96 well plate; 19.00 ± 2.00 (5 mg/ml)	Sancheti et al. (2009)
Saliaceae					
Salix mucronata Thunb.	Bark	Ethyl acetate	TLC and 96 well plate; 82.00 ± 3.90 (1 mg/ml)	ND	Eldeen et al. (2005)

Table 1. Cont'd

Sapotaceae					
Mimusops elengi L.	Flower	Methanol	TLC and 96 well plate; 32.81 ± 5.36 (0.1 mg/ml)	ND	Ingkaninan et al. (2003); Mukherjee et al. (2007 a)
Scrophulariaceae					
Bacopa monniera L.	Whole plant	Ethanol	96 well plate; 42.90 ± 1.20 (0.1 mg/ml)	ND	Das et al. (2002); Mukherjee et al. (2007 a)
Solanaceae					
Withania somnifera Dunal.	Root	Methanol	TLC and 96 well plate; 75.95 ± 0.16 (100 µg/ml)	ND	Vinutha et al. (2007)
	Root	Aqueous	TLC and 96 well plate; 24.60 ± 0.38 (100 µg/ml)	ND	Vinutha et al. (2007)
Symplocaceae					
Symplocos chinensis (Lour.) Druce	Whole plant	Methanol	96 well plate; 74.00 ± 2.00 (5 mg/ml)	96 well plate; 75.00 ± 2.00 (5 mg/ml)	Sancheti et al. (2009)
Tamariacaceae					
Myriacaria elegans Royle	Aerial parts	Methanol	96 well plate; 74.80 ± 0.00 (0.2 µg/ml)	ND	Ahmad et al. (2003); Mukherjee et al. (2007 a)
Umbelliferae					
Centella asiatica (L.) Urban	Whole plant	Hydroalcohol	96 well plate; 50% (106.55 µg/ml)*	ND	Mukherjee et al. (2007 b)
Valerianaceae					
Nardostachys jatamansi DC	Rhizomes	Methanol	96 well plate; 50% (562.21 µg/ml)*	ND	Ahmed et al. (2009)
Verbanaceae					
Lantana camara L.	Aerial parts	Aqueous	TLC and 96 well plate; 3.63 ± 1.20 (100 µg/ml)	ND	Vinutha et al. (2007)
Zingiberaceae					
Alpinia galanga Willd.	Rhizomes	Methanol	TLC and 96 well plate; 16.98 ± 0.37 (100µg/ml)	ND	Vinuta et al. (2007)
Zygophyllaceae					
Tribullus terrestris L.	Whole plants	Chloroform: methanol (1:1)	96 well plate; 37.89 ± 0.77 (1 mg/ml)	96 well plate; 78.32 ± 1.27 (1 mg/ml)	Orhan et al. (2004)
Zygophyllum fabago L.	Whole plants	Chloroform: methanol (1:1)	96 well plate; 13.25 ± 0.45 (1 mg/ml)	96 well plate; 78.37 ± 0.95 (1 mg/ml)	Orhan et al. (2004)

NI, no inhibition; ND, not done; * represents IC_{50}

acetylcholine, is considered one of the treatment strategies against several neurological disorders including AD. Several medicinal plants tested have been shown to have an inhibitory effect on AChE. Notable among such plants are several species belonging to the genus *Corydalis* (Adsersen et al*.,* 2006). Kim et al*.* (1999) found that a methanolic extract of the tuber of *Corydalis ternata* showed significant inhibition of AChE. They isolated protopine, determined the IC_{50} value to be 50 µM and showed that mice treated with protopine exhibited diminished scopolamine-induced dementia measured in a passive avoidance task. Protopine has also been isolated from the tubers of *Corydalis cava* (Preininger et al., 1976), and the aerial parts of *Corydalis solida* ssp. *tauricola* (Şener and Temizer, 1990). Berberine has been isolated from *C. ternata* and at 2.5 µM, this compound was found to have a reversible and specific AChE inhibitor effect (90%) (Hwang et al., 1996). It has been concluded that protoberberine- and protopine-type alkaloids, common compounds in *Corydalis spp*., are potent inhibitors of AChE (Adsersen et al. 2006). Plant species belonging to Fumariaceae, Papaveraceae and Ericaceae families have also been shown to have very strong activity against AChE and BChE. Since most of the acetylcholinesterase inhibitors are known to contain nitrogen, the strong activity of plants belonging to these families may be due to their rich alkaloid content (Orhan et al., 2004). Plant extracts having activities where percentage inhibition of the enzyme is 60% or more are considered to possess strong inhibitory activity (Khan et al., 2006), while moderate activity refers to percentage inhibition between 15 to 50% (Adsersen et al., 2006) and extracts having percentage inhibition of less than 15% do not show any significant inhibition of the enzyme.

A large amount of evidence has demonstrated that oxidative stress is intimately involved in age-related neurodegenerative diseases and there have been a number of studies which have examined the positive benefits of antioxidants to reduce or to block neuronal death occurring in the pathophysiology of these disorders (Ramassamy, 2006; Loizzo et al., 2009).

The anticholinesterase activities of 14 *Salvia* species were evaluated by Orhan et al. (2007). These plants were further screened for their antioxidant activity using the diphenyl picryl hydrazine (DPPH) and the xanthine oxidase (XO) inhibition assay. It was observed that the ethylacetate (EtOAc) extracts had high antioxidant activity against XO, ranging between 66.1% and 162.4%.

The EtOAc and methanol (MeOH) extracts exhibited good DPPH radical-scavenging activity, similar to that of butylated hydroxyanisole (BHA), the reference drug used. *Salvia* species have been shown to contain phenolic compounds and its antioxidant activity has been ascribed to the presence of carnosic and rosmarinic acids (Cuvelier et al., 1996; Orhan et al., 2007). Salvianolic acid, a rosmarinic acid dimer isolated from *Salvia officinalis*, had a very strong free radical-scavenging activity for DPPH and superoxide anion radicals (Lu and Foo, 2001; Orhan et al., 2007). In addition, β-sitosterol isolated from *Salvia plebeia* was also found to be a strong antioxidant by the oxidative stability instrument (OSI) (Weng and Wang, 2000; Orhan et al., 2007). Several studies on the AChE inhibitory activity of some *Salvia* species have also been reported. The essential oil of *Salvia lavandulaefolia*, together with its major components, α-pinene, 1,8-cineone, and camphor have been shown to have uncompetitive and reversible acetylcholinesterase inhibitory activity due to its monoterpenoids (Perry et al*.,* 2000; Orhan et al., 2007). In another study, four diterpenes, dihydrotanshinone, cryptotanshinone, tanshinone I, and tanshinone IIA, were isolated from the acetone extract of the dried root of *Salvia miltiorrhiza* and it was concluded that these compounds contributed to the anticholinesterase activity of the plant (Ren et al., 2004; Orhan and Aslan, 2009). These data indicate that terpenoids and monoterpenes in *Salvia* species may be responsible for their anticholinesterase activity. Several other bioactive isolated compounds with cholinesterase inhibitory activity have been reported by Houghton et al. (2006) and Hostettmann et al. (2006).

Khadri et al. (2010) evaluated the water, methanol and proanthocyanidin extracts of *C. schoenanthus* for its total phenolic content, total flavonoids and ability to scavenge the DPPH radical. The results obtained showed a high phenolic content in the three extracts with slightly higher values in the proanthocyanidinrich extracts. In addition, all the extracts were rich in flavonoids and they had very good antioxidant activity comparable to butylated hydroxytoluene (BHT), a known standard. The antioxidant activity of the plant together with its moderate inhibitory activity of acetylcholinesterase supports its medicinal use by local populations for treatment of neurodegenerative diseases. Antioxidant activity (DPPH and β-carotene-linoleic acid assays), and acetylcholinesterase inhibitory activity were determined for 10 Portuguese plants (*H. undulatum*, *M. officinalis*, *L. nobilis*, *L. pedunculata, S. minor, M. suaveolens, L. augustifolia, M. silvestris, P. argentea* and *S. officinalis)* (Ferreira et al*.,* 2006). The authors concluded that these plants may help in treating patients suffering from AD, as they showed inhibition of AChE and have very good antioxidant activity.

Loizzo et al*.* (2009) further carried out studies on the antioxidant, and anti-inflammatory activities of the essential oils of *O. ehrenbergii* and *O. syriacum* to further validate their use in the treatment of AD. Both plants exhibited significant antioxidant activity and the chemical composition of *O. syriacum* essential oil indicated that it contained antioxidant compounds such as carvacrol, carvacrol methyl ether and thymol methyl ether (Mastelić et al., 2008; Loizzo et al., 2009). Inhibition of nitric oxide (NO) production may result in anti-inflammatory activity and this was studied *in vitro* by analyzing the effect of the essential oils on chemical mediators released from macrophages. The oil of *O. ehrenbergii* showed good

anti-inflammatory activity which is probably due to the presence of thymol, one of the major components of the oils which has a phenolic structure, and has been credited with a series of pharmacological properties, including antimicrobial, antioxidant and anti-inflammatory effects (Braga et al., 2006; Loizzo et al., 2009). These results showed that both oils provide interesting properties from a functional perspective in the prevention of neurodegenerative disorders.

Chattipakorn et al. (2007) carried out additional *in vivo* studies on *Tabernaemontana divaricata* using male Wistar rats, after confirming its cholinesterase inhibitory activity *in vitro*. The major finding of this study was that the plant can inhibit neuronal AChE activity in an animal model and that it has cortical AChE inhibitory effects. According to the authors, there are several possible active compounds with AChE inhibitory activity in *T. divaricata* which include at least forty-four alkaloids and non-alkaloid constituents such as triterpenoids, steroids, flavonoids, phenyl propanoids and phenolic acids. The inhibitory effects of AChE activity in the animal model could be due to the effects of mixed alkaloids in *T. divaricata.*

The 96-well microplate and thin layer chromatography assays based on Ellman's method were the two most commonly used methods for detecting AChE and BChE inhibitory activity in the studies conducted. This is probably because these two methods ensure the possibility of running several replicates for each determination, to improve statistical treatment of results, and are both economical, as only small amounts of reagents and test substances are used.

Methanol was observed to be the most commonly used solvent in extracting the plants. This may indicate that most of the compounds which show anticholinesterase activity are polar in nature. The plant part most commonly investigated was the aerial parts or whole plant (in case of herbs), indicating that roots or bark do not contain sufficient anticholinesterase inhibitory activity.

CONCLUSION

Present efforts aimed at the treatment of Alzheimer's disease, senile dementia, ataxia, myasthenia gravis and Parkinson's disease are centered around the reduction of cholinergic deficit by the use of AChE and BChE inhibitors. Several drugs are on the market, including the plant alkaloid galanthamine. However, a search for more efficient agents with fewer side effects has resulted in the screening of several medicinal plants for possible activity as shown in this review. It is easy to perceive the potential in these plants as attractive targets for future studies, to identify the active constituents and possibly to uncover new alternatives to the existing therapies for neurodegenerative diseases. Furthermore, *in vivo* activity of the active compounds needs to be determined in animal models and human subjects, so as to determine their efficacy in a metabolic environment. Such future studies will be necessary to expand the existing, limited therapeutic arsenal for the majority of neurodegenerative diseases, especially for those therapies with side effects that limit their effectiveness.

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