



## Review Article

### AN ANCIENT APPROACH BUT TURNING INTO FUTURE POTENTIAL SOURCE OF THERAPEUTICS IN ALZHEIMER'S DISEASE

Singh Vyoma\*

Department of Biotechnology, MITS, Gwalior, MP, India

\*Corresponding Author Email: vy.biotech@gmail.com

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#### ABSTRACT

Dementia is one of the ages related mental problems and characteristic symptom of various neurodegenerative disorders including Alzheimer's disease which is age related. It is a progressive, neurodegenerative disorder which primarily affects the elderly population and it is considered to be responsible for 60 % of all dementia in people who are aged 65 or more. It is debilitating in nature, and due to which an enormous social and economic worry is placed on our society. Currently there is no proper 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 time period. Therefore there is a need for a different approach to the treatment of these diseases. Plants have been used since ancient times in the treatment of various diseases including cognitive disorders, such as alzheimer's disease. Therefore ethno pharmacological screening of plants may provide useful leads in the discovery of new drugs for the treatment of alzheimer's disease. Screening of various plants is reviewed in this article, belonging to various families, used in traditional systems of medicine (e.g. Chinese, Indian and European) for treatment of cognitive dysfunction. Phytochemical substances such as alkaloids, biphenolic lignans, curcuminoids, caffeic acid derivatives, triterpenoids, and withanolides with pharmacological activities relevant to AD treatment are discussed in this review.

**Keywords:** Phytochemicals, phytomedicine, antioxidant, anti-inflammatory activity, Amyloid peptide, cholinesterase inhibition, ethno pharmacology, iron chelation, lipid peroxidation, traditional medicine, Memory loss.

#### INTRODUCTION

Alzheimer's is a disease which, damages and kills brain cells. It is a complex disease likely caused by a combination of factors such as infection or reduced circulation, and along with to those who are genetically susceptible. Although all the contributing factors are not known yet, but scientists have identified several common threads which link the factors which are responsible for AD disease. They include Age, Heredity, Genetic history, Lifestyle, Sex, Head injury, Head size, vascular risk factors and Diet<sup>1-4</sup>. Currently, there is no cure for Alzheimer's disease. Doctors sometimes prescribe drugs to improve symptoms that often accompany Alzheimer's, including sleeplessness, wandering, anxiety, agitation and depression. The drugs currently used are tacrine hydrochloride (Cognex)<sup>5-7</sup> and donepezil hydrochloride (Aricept)<sup>8,9</sup>, rivastigmine (Exelon)<sup>10,11</sup> and galantamine (Reminyl)<sup>12,13</sup>. Cognitive disorders like Alzheimer's disease, amnesia, depression and schizophrenia are associated with impairments in learning and memory<sup>14</sup>. Poor memory, lower retention, and slow recall are common problems in today's stressful and competitive world, especially with associated ageing process. Alzheimer's disease (AD) is frequent in elderly people, as a result of malfunctioning of different biochemical pathways<sup>15</sup>, aging represents the most important risk factor for (AD)<sup>16</sup>. Age, stress, emotions are conditions that may lead to memory loss, amnesia, anxiety, high blood pressure, dementia, or to more ominous threats like schizophrenia and Alzheimer's disease<sup>17</sup>. Utilization of plants in disease remedy dates back to man's creation. Forest based rural populations have relied on medicinal plants for centuries to meet their health care needs. The non-availability of modern healthcare delivery system in most rural communities of sub Saharan Africa has propelled the people to depend on plants to solve various health challenges from simple to complex situations. In Nigeria, about 80 % of the population live in rural areas and rely on herbal and traditional medicine for their health care needs<sup>18</sup>. Plants have been used for their medicinal properties from ancient times, but now a day's plants are being also exploited for their various properties like phytomedicine, antioxidant, pesticidal, fungicidal, herbicidal etc.

Medicinal plants can be used in different forms: as raw materials for extraction of active compounds or for extraction of abundant but inactive constituents which can be transformed by partial synthesis into active compounds, and also such as or as extracts or as traditional preparations. Medicinal plants are a therapeutic resource much used by the traditional population of the world specifically for the health care. World-wide interest in the use of medicinal and aromatic plants is increasing. Beneficial effects of plant based medicines and other plant based products are being rediscovered. Ethno botanical information is leading to the discovery of novel phytopharmaceuticals or say phytomedicines and other phytoproducts.

The efficacies of some of these plants have been validated by scientific findings<sup>19</sup> though the toxicity of many is yet to be determined. There are numerous bioactive compounds used in Western medicine that have been directly isolated from plants, or are derivatives of compounds from plant sources<sup>20</sup>.

#### Plants and their phytochemicals for alzheimer's therapy

##### *Acorus calamus* L. (Araceae)

The plant *A. calamus* commonly known as sweet flag; is a perennial herb which grows mainly in swamps, marshes and river banks. In Ayurvedic medicine, the rhizome has been used for the treatment of memory loss<sup>21</sup>. Two rhizome extracts, ethanolic and hydroethanolic, exerted sedative and neuroprotective effects *in vivo* respectively<sup>21,22</sup>.

##### *Areca catechu* L. (Aracaceae)

The alkaloid arecoline is isolated from the betel nut of *Areca catechu* L. (Aracaceae), is used as a masticatory throughout the Indian subcontinent and other parts of south East Asia. Administration of arecoline resulted in improvement of memory in rats<sup>23</sup>. Arecoline has exhibited muscarinic (M<sub>2</sub>) binding activity<sup>24</sup>. In a clinical study arecoline demonstrated memory

enhancing effect in AD patients<sup>25</sup>. Despite initial success with *in vitro* studies the compounds failed to improve the cognitive functions in mild to moderate AD patients. However, research on synthetic analogue of arecoline such as Lu 25-109 (24) and talsaclidine (25) appears to be promising<sup>26</sup>.

#### ***Angelica archangelica* L. (Umbelliferae)**

*A. archangelica* is a perennial herbaceous plant used in traditional Chinese medicine (TCM) for treatment of cerebral diseases<sup>27</sup>. An ethanol extract of the dried plant roots was capable of displacing nicotine from nicotine binding receptors in a concentration-dependent manner<sup>28</sup>. It was showed that a dichloromethane subfraction of a methanol extract inhibited AChE activity *in vitro*<sup>29</sup>.

#### ***Bacopa monniera* Wettst. (Scrophulariaceae)**

*B. monniera*, 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 Jananimab<sup>30</sup>. Ethanol extracts of aerial parts and rhizome from the plant possessed nootropic activity<sup>31-33</sup>. 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<sup>34</sup>. Alternative propositions include: (i) enhancement of protein kinase activity in the hippocampus<sup>35</sup> and (ii) cognitive enhancement via its modulatory effect on the cholinergic system<sup>31</sup>. It was 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<sup>36</sup>. A similar extract of the plant demonstrated antioxidant activity in the rat frontal cortex, striatum and hippocampus<sup>37</sup>. A methanol extract of the plant inhibited NO-induced toxicity and prevented hydrogen peroxide-induced DNA cleavage *in vitro*<sup>38,39</sup>. Bacosides, which are dammarane triterpenoid saponins isolated from *Bacopa monniera*, showed nootropic activity<sup>32,33</sup>. These compounds such as bacoside, demonstrated *in vitro* antioxidant activity<sup>40</sup>.

#### ***Biota orientalis* L. (Coniferae) Cupressaceae**

The plant *B. orientalis* 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<sup>41,42</sup>. In a study carried out, S-113m (a herbal preparation composed of *B. orientalis*, *Panax ginseng* and *Schizandra chinensis*) preferentially improved memory registration and consolidation in mice<sup>43</sup>. An ethanol extract of *B. orientalis* seeds improved memory dysfunction induced by amygdala and basal forebrain lesions in mice<sup>41,44</sup>.

#### ***Celastrus paniculatus* Willd. (Celastraceae)**

The plant *C. paniculatus*, commonly known 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<sup>45,46</sup>. The seeds and seed oil have been used in AM as a memory enhancer and it was reported that the seed oil reduced the levels of noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) *in vivo*<sup>45,47</sup>. In another study, the seed oil reversed scopolamine-induced task deficit, it was reported that treatment of mentally retarded children with the oil produced an improvement in their IQ scores<sup>46,48</sup>. An aqueous seed extract from *C. paniculatus* have been shown antioxidant effect in rat brain, which may be contribute to cognitive enhancing activity observed *in vivo*<sup>49</sup>. It was reported that a methanol extract of the inflorescences showed anti-inflammatory effect which may be relevant to AD therapy<sup>50</sup>. A methanol extract was assessed for N-methyl-D-aspartate (NMDA) and  $\gamma$ -aminobutyric acid (GABA) binding activities and nerve growth factor (NGF) effects but did not show any response<sup>51</sup>. A possible

explanation may be that the extraction solvent was polar and seed oil and hydrophobic constituent may be responsible for the cognitive enhancing effects of *C. paniculatus*.

#### ***Centella asiatica* L. (Umbelliferae)**

*C. asiatic* 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<sup>52</sup>. In TCM, it is also used to combat physical and mental exhaustion<sup>53,54</sup>. 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<sup>55</sup>. Aqueous extract of the whole plant enhanced cognitive function in rats, which was associated with the *in vivo* antioxidant activity of the extract<sup>56</sup>. An aqueous leaf extracts modulated dopaminergic, serotonic and adrenergic systems *in vivo* and improved learning and memory<sup>57</sup>. The essential oil from the plant is reported to contain monoterpenes e.g.  $\beta$ -pinene and  $\gamma$ -terpinene<sup>54</sup>, which have demonstrated AChE inhibitory activity, though not as potent as the standard reference substance<sup>58</sup>.

#### ***Clitoria ternatea* L. (Leguminosae)**

*C. ternatea*, commonly known as butterfly-pea, is a persistence herbaceous perennial legume. The rhizome has been used in AM as a brain tonic and is reputed to promote memory and intellect<sup>59</sup>. In a study, 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<sup>60</sup>. 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<sup>61</sup>. An ethanol extract obtained from the stem, flowers, leaves and fruits of the plant were reported to be sedative in mice<sup>62</sup>.

#### ***Codonopsis pilosula* Franch. (Campanulaceae)**

*C. pilosula*, 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<sup>62</sup>. 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<sup>63</sup>.

#### ***Convolvulus pluricaulis* Chois. (Convolvulaceae)**

*C. pluricaulis*, 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<sup>33</sup>. The whole plant in the form of a decoction is used with milk and cumin to treat fever, disability, memory loss, syphilis, and scrofula<sup>64</sup>.

#### ***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, di-chloromethane and methanol extracts demonstrated AChE inhibitory activity<sup>29</sup>. It was reported that a methanol extract of the rhizome possessed NGF-enhancing activity<sup>65</sup>. Methanol extracts of the plant are reported to have MAO inhibitory activity and nootropic activities *in vivo* and *in vitro* antioxidant activity<sup>66-68</sup>. It was also reported that an aqueous extract showed *in vitro* antioxidant activity<sup>69</sup>. An ethanol extract of the whole plant demonstrated anti-inflammatory effect *in vivo*<sup>70</sup>. Alkaloids berberine, coptisine and palmatine isolated from *Coptis chinensis* possessed AChE inhibitory and NGF-enhancing activities *in vitro*<sup>65</sup>.

***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<sup>71-72</sup>. This may have been achieved by the inhibiting the impairment of hippocampal synaptic plasticity<sup>73</sup>. A hydroalcoholic extract of dried stigmas inhibited A $\beta$  fibrillogenesis and exerted antioxidant effect *in vitro*<sup>74</sup>. Crocin (34) isolated from *Crocus sativus* demonstrated cognitive enhancing activity in mice<sup>71-72</sup>. The compound possessed *in vitro* antioxidant and anti amyloidogenic properties<sup>74</sup>; furthermore it suppressed TNF -induced apoptosis *in vitro*<sup>75</sup>.

***Curcuma longa* L. (Zingiberaceae)**

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<sup>76</sup>. Antidepressant activity is of significant importance in the management of AD.

***Curcuma longa***

Curcuminoids from *Curcuma longa*; curcumin, demethoxycurcumin, bisdemethoxy curcumin and calebin-A (and some of its synthetic analogues), showed neuroprotective activity against A  $\beta$ -induced toxicity<sup>77-78</sup>. It was suggested that this activity may be due to an antioxidant effect<sup>79</sup>. Among the curcuminoids present in *C. longa*, curcumin has been the subject of most research<sup>80</sup>. The antioxidant activity of curcumin has been reported in various studies<sup>81-84</sup>. It demonstrated neuroprotective activity against ethanol-induced brain injury *in vivo*. It was reported that this effect was related to its *in vivo* antioxidant activity<sup>85</sup>. A number of studies have demonstrated that curcumin possesses anti-inflammatory activity<sup>86-88,84</sup>. Using computational software it was demonstrated that curcumin as a result of containing an enolic centre and two phenolic polar groups separated by a conjugated hydrocarbon chain, exhibits unique hydrophobic and hydrophilic features. The former property facilitates its partition into the blood brain barrier and the later enables its binding to the A peptide. Further studies also show that the enol isomer has all the properties for an ideal antioxidant<sup>89</sup>.

***Evodia rutaecarpa* (Juss.) Benth. (Rutaceae)**

*E. rutaecarpa* is a deciduous small tree that is used in TCM for cardio tonic, restorative and analgesic effects<sup>90-91</sup>. There are also TCM prescriptions which have been used in CNS disorders. A TCM preparation, Oren-gedoku-to, demonstrated antioxidant<sup>92-94</sup>, anti-inflammatory<sup>95-97</sup> and neuroprotective<sup>98-99</sup> 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<sup>100</sup>. A dichloromethane extract of *E. rutaecarpa* strongly inhibited AChE *in vitro* and reversed scopolamine-induced memory impairment in rats<sup>29</sup>. Dehydroevodiamine strongly inhibited AChE *in vitro* and reversed scopolamine-induced memory impairment in rats<sup>29</sup>. Dehydroevodiamine increased cerebral blood flow *in vivo*, which may contribute to the nootropic activity of the compound<sup>101</sup>. Rutaecarpine, isolated from *E. rutaecarpa* inhibited COX-2 activity *in vitro* and exerted anti-inflammatory effect *in vivo*<sup>102-103</sup>.

***Ginkgo biloba* L. (Ginkgoaceae)**

*G. biloba* is dioecious perennial tree that is indigenous to East Asia, which has been used in TCM for the improvement of memory loss

associated with abnormalities in the blood circulation<sup>104</sup>. 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<sup>105-108</sup>. 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<sup>33</sup>. EGb 761 showed cognitive enhancing activity in number of clinical studies<sup>105-107,109</sup>. The extract showed neuro protective effect against A  $\beta$  and nitric oxide (NO) induced toxicity in the neuronal cell culture<sup>110-111</sup> and could reduce apoptosis both *in vitro* and *in vivo*<sup>112-113</sup>. EGb 761 showed protective effect against ischaemia-induced neurotoxicity<sup>114</sup>. The extract also demonstrated *in vitro* and *in vivo* antioxidant activities<sup>115-117</sup>. The extract improved blood supply to the brain, thereby ensuring its efficient functioning and enhanced cognitive performance<sup>118-119</sup>, Modulation of muscarinic cholinergic system enhanced performance of spatial task<sup>120</sup>.

***Ginkgo biloba***

In addition to flavonoids, there are terpene lactones, i.e. bilobalide and ginkgolides present in *Ginkgo biloba*; that have been classified as nootropic agents<sup>33</sup>. Some of the research showed that bilobalide, was successful in inhibiting phospholipids breakdown and cholinesterase release under hypoxic conditions<sup>121</sup>. 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<sup>122</sup>. 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<sup>123</sup>. Bilobalide showed protective effect against ischaemia-induced neurotoxicity<sup>114</sup>. It was reported that ginkgolides alleviates A induced pathological behaviour<sup>124</sup>. Ginkgolide B demonstrated neuroprotective activity against A  $\beta$  induced toxicity<sup>125</sup>. Ginkgolides also reversed A $\beta$  suppression of ACh release *in vivo*<sup>126</sup>. It should be mentioned that despite the structural similarities between ginkgolides and bilobalide, few analogies between their CNS activities profiles can be detected<sup>33</sup>. In a structure activity study, it was indicated that the difference in the existing molecular space around the (tert)-butylated substituted cyclopentane ring dictate their activity profile<sup>127</sup>.

***Hypericum perforatum* L. (Clusiaceae) (Hypericaceae)**

*H. perforatum* commonly known as St. John's Wort is a herbaceous perennial plant that has been used in Portuguese and Turkish folkore medicine for the treatment of neurological disorders<sup>128</sup>. The dried crude herb standardised to hypericins improved memory and learning dysfunction, it is also reported that a standard extract of *H. perforatum* (hypericin) possessed neuroprotective activity<sup>129,131</sup>. It is reported that extracts of *H. perforatum*, which have been standardised to hypericin and hyperforin respectively, showed *in vitro* antioxidant activity<sup>132-133</sup>, *in vivo* anti-inflammatory effects<sup>134</sup>. Hydroalcoholic extracts of aerial parts of *H. perforatum* demonstrated nootropic activity *in vivo*, which may due to adrenergic ( $\alpha$  and  $\beta$  receptor) and serotonergic (5HT1A) antagonistic activity suggested that a hydroalcoholic extract of the plant could reduce the rate of degradation of Ach<sup>135-138</sup>.

***Magnolia officinalis* Rehd. and Wils. (Magnoliaceae)**

*M. officinalis* 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*<sup>139-143</sup>. It is demonstrated that the *in vitro* antioxidant activity of various Soxhlet and supercritical fluid extracts, with the ethyl acetate-soluble Soxhlet extract being the most active<sup>144</sup>. 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*<sup>145</sup>. Both the compounds showed *in vivo* antioxidant activities<sup>139</sup>. Magnolol demonstrated *in vitro* neuroprotective effect<sup>146</sup>. The compound also showed anti-inflammatory activity *in vitro* and *in vivo*<sup>147-148</sup>. It is demonstrated that honkiol exerted *in vivo* anti-inflammatory effect by inhibiting ROS formation<sup>149</sup>.

#### ***Marsilea quadrifolia***

It is a creeping perennial herb and is able to adapt to low light and high light conditions. It has various medicinal properties like plant pacifies vitiated pitta, cough, bronchitis, psychiatric diseases, eye diseases, diarrhoea, skin diseases, antidote, antiphlogistic, depurative, diuretic and febrifuge. The ethanolic extract of plant *Marsilea* significantly improved the learning and memory in mice. The anti-oxidant property and the presence of steroids of *Marsilea quadrifolia* may be contributing favourably to memory enhancement effect. Since scopolamine induced amnesia was reversed by *Marsilea*, it is possible that the beneficial effect on learning and memory was due to facilitation of cholinergic transmission in mouse brain. *Marsilea quadrifolia* has shown promise a memory enhancing agent in all laboratory models employed<sup>224</sup>.

#### ***Melissa officinalis* L. (Lamiaceae)**

*M. officinalis*, 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<sup>28,91,150</sup>. The volatile oil has been reported to possess *in vitro* AChE inhibitory<sup>28,151</sup> and antioxidant activities<sup>151-153</sup>. Its constituent monoterpenes were reported to possess weak AChE inhibitory activity<sup>154</sup>, while it has been suggested its anti oxidant activity is due to presence of oxygenated monoterpenes and sesquiterpene hydrocarbons<sup>152</sup>. A wide range non-polar and polar extracts have displayed antioxidant activity<sup>151,155-159</sup>. In case of polar extracts, it has been proposed that the active constituents contributing to the activity of the extracts are the polyphenolic substances<sup>158-159</sup>. Ethanol and decoction extracts of aerial parts of the plant also showed *in vitro* AChE inhibitory activity<sup>151</sup>. Ethanol extracts obtained from the leaf material were reported possessed nicotine and muscarinic receptor binding properties<sup>28,160</sup>. A methanolic extract of the plant leaves was clinically capable of improving the mood and accuracy of attention<sup>161</sup>. However, there was a decline in memory function. Furthermore, *in vitro* nicotinic and muscarinic binding were low in comparison to that found by<sup>160</sup>. This difference may be due to loss of volatile component during the manufacturing process<sup>160</sup>. According to the reports of<sup>160-161</sup>, a clinical study was conducted in which, a hydroalcoholic leaf extract was effective in improving cognitive functions in mild to moderate AD patients<sup>162</sup>.

#### ***Piper methysticum* Frost. (Piperaceae)**

*P. methysticum*, commonly known as Kava, is a perennial shrub that has been used in Polynesia, Melanesia and Micronesia occupies in preparation of a drink to be consumed for ritual and social purposes<sup>163-164</sup>. In a clinical trial carried out, a standardised rhizome extract (kavalactones) elevated the mood and enhanced cognition performance<sup>165</sup>.

#### ***Polygala tenuifolia* Wild. (Polygalaceae)**

*P. tenuifolia*, commonly known 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<sup>53</sup>. 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<sup>166-169</sup>. *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. 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<sup>170-171</sup>. It was demonstrated in a clinical study that KUT treatment in AD patients improved memory-related behaviour<sup>171</sup>. It is suggested that, cinnamic acid derivatives may be contributing to the beneficial effects of KUT<sup>170</sup>. A dichloromethane subfraction of a methanol rhizome extract demonstrated *in vitro* AChE inhibitory activity<sup>29</sup>. In another study, an ethanol rhizome extracts improved cognitive dysfunction and exerted protective effect against glutamate and APP toxic metabolites induced neurotoxicity *in vitro*<sup>78</sup>. Aqueous extract of the rhizome showed *in vitro* anti-inflammatory properties<sup>172-173</sup>, the aqueous extract also demonstrated tranquilizing activity<sup>174-175</sup>.

#### ***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<sup>176</sup>. The dried rhizome of rhubarb has been used in TCM for the treatment of blood stagnation syndrome<sup>177</sup>. In a study carried out, a methanol extract obtained from the rhizome of Korean rhubarb, *Rheum undulatum* and demonstrated *in vitro* antioxidant activity<sup>78</sup>. 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<sup>177</sup>.

#### ***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<sup>179</sup>. Volatile oil obtained from *S. lavandulaefolia* showed strong AChE inhibitory activity<sup>28</sup>. The activity is believed to be due to the presence of the cyclic monoterpenes 1,8-cineole and  $\alpha$ -pinene, with some contribution from other constituents perhaps by acting synergistically. Administration of *S. lavandulaefolia* volatile oil decreased AChE activity *in vivo*<sup>180</sup>. Components of the oil were also screened for antioxidant activity. 1,8-Cineole,  $\alpha$ -pinene and  $\beta$ -pinene exerted antioxidant effect, however, camphor showed pro-oxidant activity<sup>180</sup>. The ethanol *S. lavandulaefolia* extract showed weak activity when compared against antioxidant propyl gallate. Water and chloroform subfractions of this extract demonstrated similar activity<sup>180</sup>. An ethanol extract of the plant demonstrated *in vitro* anti-inflammatory properties<sup>180</sup>. In a clinical study carried out by<sup>181</sup>, administration of a standardised essential oil extract resulted in mood elevation and improvements of memory.

#### ***Salvia miltiorrhiza* Bung. (Lamiaceae)**

*S. miltiorrhiza*, 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<sup>174,182</sup>. It is reported that a methanol extract of the plant demonstrated *in vitro* anti-inflammatory activity<sup>183</sup>. The extract was fractionated further and among the entire fractions ethyl acetate fraction displayed the strongest anti-inflammatory activity. In a study carried out, the methanol extracts improved cognitive dysfunction in rats<sup>66</sup>. Aqueous leaf and rhizome extracts of the plant, demonstrated *in vitro* antioxidant properties<sup>184-185</sup>. Salvianolic acids A and B isolated from *Salvia miltiorrhiza* offered protection against cerebral ischemia induced memory impairment in mice, it is reported that salvianolic acid B prevented A induced neurotoxicity *in vitro*<sup>186-187</sup>. This effect was accompanied by decreased formation ROS, suggesting the antioxidant activity being behind the neuro-protective effect. Rosmarinic (32) a well known antioxidant isolated from



*Salvia* and other Lamiaceae species<sup>159,188-189</sup>, demonstrated *in vitro* protective effect against A induced neurotoxicity<sup>190</sup>. Sinapic acid (33) isolated from *Polygala tenuifolia* increased the activity of ChAT in the frontal cortex of brain lesioned rats<sup>170</sup>.

#### Phytochemical:

##### Tanshinones

Tanshinones isolated from *S. miltiorrhiza*, viz., tanshinone I, dihydrotanshinone, methylenetanshinone and cryptotanshinone, demonstrated significant antioxidant effect in lard<sup>191-192</sup>. Tanshinone I, dihydrotanshinone, and cryptotanshinone showed anti-inflammatory activity *in vitro* and *in vivo*<sup>193-194</sup>. It is demonstrated that tanshinone I and tanshinone IIA, dihydrotanshinone, cryptotanshinone, exerted AChE inhibitory activity *in vitro*<sup>195</sup>. Tanshinone improved changes induced by A $\beta$  (1-42) in rats, including a decrease in AChE positive fibres<sup>196</sup>. A screening method based on A $\beta$  induced neurotoxicity, have been used to identify A $\beta$  -peptide inhibitor, tanshinone IIA<sup>197</sup>. Both the screening method and the inhibitor have been patented in China<sup>197</sup>. 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. miltiorrhiza* has proved promising.

##### *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<sup>179</sup>. Essential oil obtained from the plant exhibited *in vitro* AChE and BuChE inhibitory activities<sup>28,198</sup>. It is reported that hexane and ethyl acetate extracts of the plant showed *in vitro* anti-inflammatory properties<sup>199</sup>. In another study hexane and chloroform extracts of the leaves were reported to possess *in vivo* anti-inflammatory activity, it is demonstrated that ethyl acetate, acetone extracts obtained from the aerial parts of the plant possessed *in vitro* antioxidant properties<sup>200-201</sup>. Methanol extracts of the leaf material and the aerial parts also showed *in vitro* antioxidant activity<sup>202-203</sup>. Ethanolic leaf extract of *S. officinalis* demonstrated *in vitro* AChE and BuChE inhibitory activities<sup>28,204</sup>. A hydroalcoholic extract from the leaves demonstrated *in vitro* protective effect against A induced neurotoxicity<sup>190</sup>. In a clinical study carried out, a hydroalcoholic leaf extract was effective in the management of mild to moderate AD<sup>205</sup>. Aqueous extracts of the leaves, obtained by hydrodistillation and hot water extraction displayed *in vitro* antioxidant activity<sup>206-207</sup>.

##### *Terminalia chebula* L. (Combretaceae)

The ripe fruit of *T. chebula* is reputed to enhance memory and to promote longevity<sup>59,52</sup>. 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<sup>51</sup>. In a study carried out, the aqueous extract of dried fruits *T. chebula* demonstrated *in vitro* antioxidant activity<sup>208</sup>.

##### *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<sup>209</sup>. Administration of the standardised root extracts improved cognitive dysfunction *in vivo*<sup>210-211</sup>. A hydroalcoholic extract of the roots standardised for withanolides and withanoles showed neuroprotective effect *in vivo*<sup>212</sup>. Hydroalcoholic and ethanolic root extracts demonstrated *in vitro*

and *in vivo* antioxidant and anti-inflammatory properties<sup>213-215</sup>. A methanol root extract promoted the formation of dendrites in a culture of human neuroblastoma cells<sup>216-217</sup>, it is reported that the methanolic extract possessed *in vivo* antioxidant properties. *W. somnifera* root powder demonstrated *in vivo* antioxidant and anti-inflammatory effects<sup>218</sup>.

##### Withanolides

There have been numerous studies on *W. somnifera* and its constituents. The sitoindosides IX and X isolated from the plant, augmented learning acquisition and memory in both young and old rats<sup>219</sup>. 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 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<sub>1</sub> receptor binding in the lateral and medial septum and in frontal cortices, and increased muscarinic M<sub>2</sub> receptor binding sites in the cortical regions<sup>220</sup>. The mixture improved ibotenic acid- induced cognitive dysfunction and reduction in the cholinergic markers in rats<sup>221</sup>. 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*<sup>214,222-223</sup>.

#### CONCLUSION

Alzheimer's disease is a neurodegenerative disorder currently without an effective treatment. Impairment of memory is the initial and most significant symptom of AD. AD is associated with a decline in cognitive abilities. 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 generally from the rhizome, seeds and aerial parts etc. of the plants. The phytochemical constituents contributing to the activity have been isolated. These include alkaloids, and tri- terpenoids. The non polar extracts and essential oils from *C. asiatica*, *Melissa officinalis*, *Marsilea quadrifolia* and *Salvia* species possessed antioxidant and anti-inflammatory properties. 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 cinnamic acid derivatives, triterpenoid saponins, bacosides, curcuminoids, zeatin, crocin. Based on phytochemical and pharmacological studies carried out there are several phytoconstituents which can be potential drug targets for AD treatment. These include crocin, curcumin, hyperforin, hypericin, magnolol, sinapic acid, tanshinones, salvianolic acids, arecoline and pilocarpine. Therefore, it can be concluded that extracts of medicinal plants having a wide range of polarity and different classes of phytochemical substances, have demonstrated and tried to prove pharmacological activities relevant to the treatment of AD.

#### ABBREVIATIONS

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

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