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Review Article

GLOBAL BURDEN OF ALZHEIMER'S DISEASE AND PROMISING POTENTIAL OF HERBAL MEDICINES

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ABSTRACT

With the ageing of the population, Alzheimer's disease (AD) represents an individual and public health problem of enormous significance. Research is ongoing worldwide in the search for more effective treatments, including drugs to slow or prevent progression in AD. There are only four drugs that the Federal Drug Administration (FDA) has approved and that are currently available for treating AD patients in the United States. Three of the drugs-Tacrine (CognexR), Donepezil (AriceptR), and Rivastigmine (ReminylR)-inhibit acetylcholinesterase (AChEI) either selectively or non-selectively, but they have resulted in various adverse drug effects. Memantine (NamendaR), the fourth and most recently approved drug, non-competitively inhibits NMDA receptors, prevents glutamate excitotoxicity, and shows minimal adverse drug effects in AD patients. Other drugs are available for the secondary management of behavioural and psychological symptoms associated with AD. Recently, herbal drugs have been systematically tested in animal and cell models of AD and, to lesser extent, in clinical trials. Herbal drugs are relatively less toxic, can readily cross the blood brain barrier, and are bioavailable to exert multiple synergistic effects, including improved cognitive functions. This article reviews the global burden of AD, problems with synthetics drugs and potentials of herbal plants/phytoconstituents in AD.

INTRODUCTION

Alzheimer's disease (AD) was first described by the German psychiatrist, Alois Alzheimer, in 1907. The disease appeared less common in the early decades of the 20th century. Now a day, however, dementia is a very common illness in the elder persons. The initiating molecular event(s) of AD is not known, and its pathophysiology is highly complex. The neuropathological hallmarks of AD are the accumulation of extracellular amyloid plaque containing β-amyloid and intracellular neurofibrillary tangles containing polymerized and hyperphosphorylated tau protein (Martin, 1999). In recent years much attention has been focused on free radical injury as a fundamental pathophysiologic mediator of tissue injury in

human diseases, including AD. An estimated 35.6 million people worldwide will be living with dementia in 2010 (Table 1.1). This number is estimated to nearly double every 20 years, to 65.7 million in 2030, and 115.4 million in 2050 (Prince and Jackson, 2009). Much of the increase is clearly attributable to increases in the numbers of people with dementia in low and middle income countries.

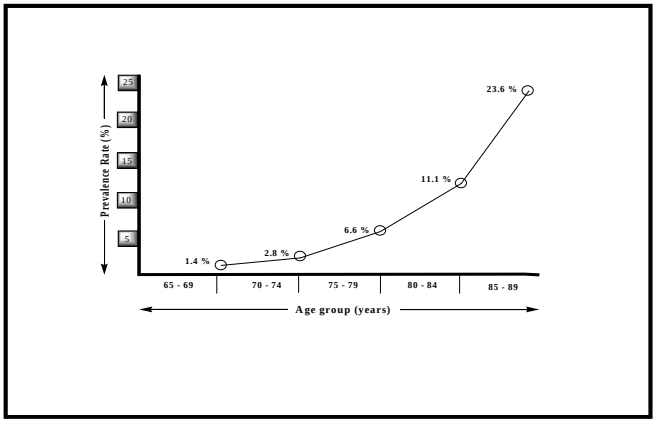

Fig. 1.1: Relationship of age and progression of Alzheimer's disease (WHO, 2006)

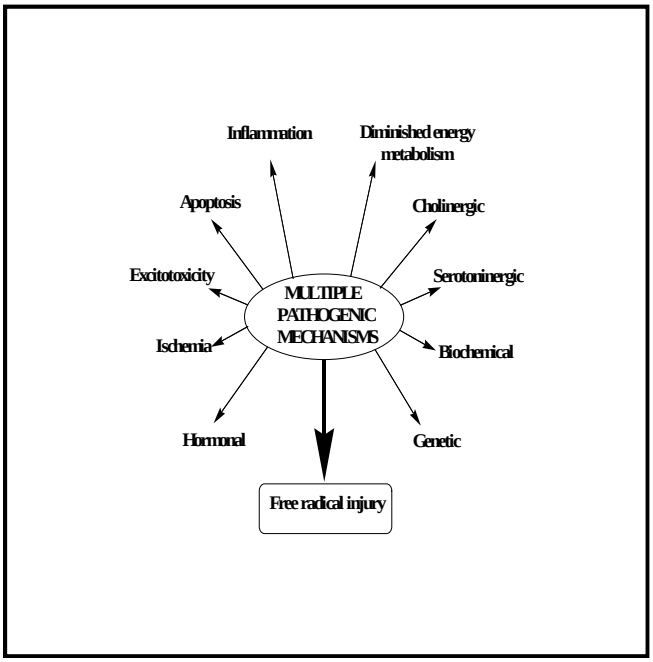

Fig. 1.2: Probable pathophysiological mechanisms of Alzheimer's disease.

The global cost of dementia

A research group from Sweden's Karolinska Institute has attempted to estimate the worldwide cost of dementia in 2005 (Wimo *et al*., 2006; Wimo *et al*., 2007). This amounts to US $ 315 billion per year, of which US $ 227 billion (72% of the worldwide total) is contributed by high income countries and US$88 billion (28% of the total) by low and middle income countries. It can be seen that informal (family) care is more often used in resource-poor countries, where few formal health or social care services are available (Prince *et al.*, 2007). Informal care accounts for 56% of costs in low income countries, 42% in middle income countries, and 31% in high income countries (Kalaria *et al.*, 2008). Annual costs per person with dementia ranged from US$1,521 for low income countries, to US $ 4,588 in middle income countries, and US $ 17,964 in high income countries.

Table 1.1: Estimation of prevalence of dementia from 2010 to 2050 (Prince and Jackson, 2009).

Global Burden of Disease (GBD) Region	Over 60 population (millions)	Crude estimated prevalence (%)	Number of people with dementia (millions)			Proportionate increases (%)	
	2010	2010	2010	2030	2050	2010-2030	2010-2050
ASIA	406.55	3.9	15.94	33.04	60.92	107	282
EUROPE	160.18	6.2	9.95	13.95	18.65	40	87
AMERICAS	120.74	6.5	7.82	14.78	27.08	89	246
AFRICA	71.07	2.6	1.86	3.92	8.74	111	370
WORLD	758.54	4.7	35.56	65.69	115.38	85	225

Current approaches in the treatment of AD

The proposed pathogenic mechanisms for AD generally comprise the basis for current attempts at therapeutic intervention. These include loss of cholinergic function (cholinergic replacement therapy and neurotropins), oxidative stress (antioxidant therapy), the amyloid cascade (Aβ vaccine, γ-secretase effectors, statins), inflammatory mediators (NSAIDs), steroid hormone deficiencies (hormone replacement therapy), excitotoxicity (memantine), and the role of dietary factors (low saturated fat diets, moderate alcohol intake) (Cornelius *et al.*, 2004; DeKosky *et al.,* 2008; Sabbagh, 2009; Gulyaeva *et al.*, 2010; www.clinicaltrials.gov).

Status of currently used drugs used in AD

There was no effective pharmacotherapy for Alzheimer's disease (AD) before the approval of the cholinesterase inhibitors (ChEIs) and memantine. To date, however, no new agent has successfully passed through all phases of the clinical development process (Cornelius *et al.*, 2004; DeKosky *et al.,* 2008; Sabbagh, 2009; www.clinicaltrials.gov). Because it is highly unlikely that any individual agent will provide a cure for AD, future treatment is likely to involve polypharmacy, with newer medications given in combination with ChEIs and with each other.

Herbal medicines

Currently employed medicines for AD, are frequently associated with adverse drug effects and do not cure the disease by modifying its pathology. There remains an urgent need for developing alternative approaches to AD therapeutics. A large segment of the public finds solace in herbs, in part believing that herbs are natural and hence safer than synthetic drugs, and that a complex mixture of herbs can effectively treat complex diseases. These beliefs may account for the sudden increase in herbal use in the last decade. Recently, herbal treatments have been tested in animal and cellular models of AD and in clinical trials with AD subjects. In AD animal models and cell models, herbal extracts appear to have fewer adverse effects than beneficial effects on Aβ and cognitive functions (Thimmappa *et al.*, 2005). These extracts have multi-functional properties (pro-cholinergic, anti-oxidant, anti-amyloid, and anti-inflammatory), and their use in the treatment of AD patients looks promising (Gao *et al.*, 2013). In recent decades, a number of agents were isolated from these herbs and their efficacies against AD were tested. Some flavonoids, alkaloids, phenylpropanoids, triterpenoid saponins, and polysaccharides were demonstrated to have potential efficacies against AD via targeting multiple pathological changes of this disease (Gao *et al.*, 2013). The complex pathology of AD and heterogeneous pharmacological effects of herbal extracts pose difficult challenges in the development of herbal drugs for AD treatment (Houghton, 2003). However, the number and quality of recent studies suggest that herbal drugs and AD pathology are at a new crossroad. Here, we identify herbal extracts that have been found to affect AD pathomechanisms and sympotoms of AD.

Table 1.2: Herbal drugs commonly used or referred in literature for their role in cognitive deficits or Alzheimer's disease.

S. No.	Botanical name	Aactive principle	References
1	*Scutellaria lateriflora*	Antioxidant	Lohani *et al.*, 2013
2	*Withania somnifera*	Withaferin A, Sitoindosides VII-X	Chaudhary *et al.*, 2004; Dhuley, 1997
3	*Panex ginseng*	Cholinergic activity	Reid, 1986
4	*Bacopa monniera*	Bacosides	Kishore and Singh 2005; Anbarasi *et al*., 2005
5	*Centella asiatica*	Triterpenoids, Asiaticosides	Soumyanath *et al.*, 2005; Rao *et al.*, 2006

6	*Convolvulus pluricaulis*	Antioxidants	Kumar, 2006
7	*Emblica officinalis*	Antioxidants	Satayavati, *et al*., 1997
8	*Ocimum sanctum*	Antioxidants, Antiinflammatory	Joshi and Parle, 2006; Gupta *et al*., 2002
9	*Rosmarinus officinalis*	Cholinergic, Antioxidant	Bartram, 1995
10	*Ginkgo biloba*	Ginkgolides	Kleijnen and Knipschild, 1992
11	*Melissa officinalis*	Cholinergic, Antioxidant	Orhan and Aslan, 2009
12	*Salvia officinalis*	Monoterpenoids	Oboh and Henle, 2009
13	*Angelica archangelica*	Nicotinic activity	Park *et al*., 1996
14	*Angelica sinensis*	Anticholinesterase	Park *et al*., 1996
15	*Evodia rutaecarpa*	Anticholinesterase	Park *et al*., 1996
16	*Huperzia serrata*	Huperzine	Cheng *et al*., 1996; Skolnick, 1997;
17	*Pueraria thunbergiana*	Daidzein	Heo *et al.*, 2006
18	*Thea sinensis*	Flavan-3-ol gallate esters: Epicatechin gallate, Epigallocatechin gallate, Gallic acid	Bastianetto *et al*., 2006
19	*Callicarpa dichotoma*	Acetocide	Lee *et al.*, 2006
20	*Flemingia macrophyla*	Fleminginin Flemingichromone Flemingichalcone Osajin,5,7,4'-trihydroxy-6,8-Diprenylisoflavone, 5,7,4'-trihydroxy-6,3'-diprenylisoflavone,	Shiao *et al.*, 2005
21	*Vaccinum frondosum*	Polyphenols	Lau *et al*., 2005
22	*Pueraria flos*	Thomsonide	Yamazaki *et al.*, 2005
23	*Ajuga bracteosa*	Withanolides 1, 3, 4, 5	Chaudhary *et al.*, 2005
24	*Curcuma longa*	Curcumin	Ringman *et al.*, 2005
25	*Cynanchum atratum*	Cynatroside B	Lee *et al.*, 2005
26	*Vitis winifera*	Oligonol	Li *et al.*, 2004
27	*Lycopodium clavatum*	Lycopodine, Lycodine, Fawcettimine,	Ma and Gang, 2004
28	*Nerium indicum*	Polysacharides J2, J3 and J4	Yu *et al.*, 2004

29	*Gentiana campestris*	Bellidin, Bellidifolin, Bellidin 8-O-glucopyranoside	Urbain *et al.*, 2004
30	*Cassia tora*	Alaternin, Nor-rubrofusarin glucose	Park *et al.*, 2004
31	*Scutellaria baicalensis*	Baicalein, Baicalin	Heo *et al.*, 2004
32	*Galanthus nivalis*	Galanthamine	Heinrich and Teoh, 2004
33	*Cannabis sativa*	Cannabidiol	Iuvone *et al.*, 2004
34	*Citrus junoson*	Naringenin	Heo *et al.*, 2004
35	*Zizyphus jujuba*	Cis-9-octadecenoamide	Heo *et al.*, 2003
36	*Hypericum perforatum*	Hyperforin	Griffit *et al.*, 2009
37	*Peganum harmala*	Deoxypeganine	Shi *et al.*, 2000
38	*Vinca alba*	Vinpocetine	Tamaki *et al.*, 1985
39	*Vitis winifera*	Reserveratrol	Luo and Huang, 2006
40	*Zingiber officinale*	[6]-gingerol	Joshi and Parle, 2006
41	*Piper nigrum*	Piperine	Joshi and Parle, 2005
42	*Phyllanthus niruri*	Phyllanthin	Joshi and Parle, 2006
43	*Crocus sativa*	Safranal	Sadeghnia *et al.*, 2013

What makes herbs particularly suitable for treating AD?

The three most important criteria in selecting drugs for treating AD also apply to herbal drugs: the bioavailability of herbals, the ability of herbs to cross the BBB, and the lack of adverse effects associated treatments (Thimmappa *et al.*, 2005). In addition, herbal drugs appear to meet a fourth criterion: they result in a synergistic effect with the herbal

CONCLUDING REMARKS

Tremendous progress has been made in developing strategies to treat AD. Some of these strategies include anti-inflammatory, anti-amyloid, anti-oxidant, and pro-cholinergic medicines. A successful application of a therapeutic strategy in clinical trials requires a clear understanding of both the adverse and beneficial effects of the drugs. Currently available FDA-approved drugs treat AD symptomatically and provide temporary relief from dementia. However, these drugs are frequently associated with adverse drug effects and do not cure the disease by modifying its pathology. There remains an urgent need for developing alternative approaches to AD therapeutics. Recently, herbal drugs have been systematically tested in animal and cell models of AD and, to lesser extent, in clinical trials. Herbal drugs are relatively less toxic, can readily cross the blood brain barrier, and are bioavailable to exert multiple synergistic effects, including improved cognitive functions. However, chemical compositions of herbs and their potential for alleviating or reducing symptoms of AD or for affecting the disease mechanism need to be further studied (Thimmappa *et al.*, 2005). Thus, herbal drugs containing antioxidants appear to be a promising alternative medicine in treating AD patients.

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