Phcog Rev.: Review Article

Potential of Phytochemicals in management of cognitive disorders- An Update

Hanumanthachar joshi, Patil Jagadeesh & Milind Parle.

* Department of Pharmacognosy and Phytotherapy, Soniya Education Trust’s College of Pharmacy, S.R. Nagar, Dharwad, Karnataka, India.
1 Division of pharmacology, Dept. Of Pharm. Sciences, Guru Jambeshwar University of Science and Technology, Hisar, Haryana, India.

Author for Correspondence: amanjoshi17@yahoo.com

ABSTRACT

Memory function is vulnerable to a variety of pathologic processes including neurodegenerative diseases, strokes, tumors, head trauma, hypoxia, cardiac surgery, malnutrition, attention-deficit disorder, depression, anxiety, the side effects of medication, and normal ageing. Normal ageing is known to deteriorate memory in human beings. Oxygen free radicals, the harmful byproducts of oxidative metabolism are known to cause organic damage to the living system, which may be responsible for the development of Alzheimer’s disease (AD) in elderly. AD is a progressive neurodegenerative brain disorder that occurs gradually and results in memory loss, unusual behavior, personality changes and ultimately death. It is the most common form of onset of adult dementia and attention deficit disorders. Nootropics represent a new class of psychotropic agents with selective facilitatory effect on integrative functions of the central nervous system, particularly on intellectual performance, learning capability and memory. AD begins as a deficiency in the production of the neurotransmitter acetylcholine. The National Institute of Health predicts, if the current trend continues, there will be more than 8.5 million AD patients by the year 2030 in USA alone. Amnesic mild cognitive impairment represents a transitional state between the cognitive changes of normal ageing and the earliest critical features of Alzheimer’s disease. Although there is no cure for dementia of AD type at present, alternative pharmacologic treatment modalities can reduce the symptoms of cognitive impairment and slow disease progression. Presently, the allopathic system of medicine principally relies on nootropic agents, such as piracetam, aniracetam, fosractam, nefiracetam, etc., and anticholinesterases, such as Donepezil and tacrine which are commonly used for improving mood and behavior. However the Donepezil have adverse side effect on cholinergic symptoms particularly gastrointestinal symptoms like nausea, vomiting and diarrhea. Tacrine has adverse effect on liver toxicity, as shown by elevated serum amino transferases. Since allopathic system of medicine is yet provide a radical cure of AD, it is worthwhile to look for new direction, which would minimize the memory loss of patients with neuropsychiatric disorder. The utility of traditional medicines may be explored for treating patient with dementia. In this review, the phytochemicals proved to be of potential in the modulation of cognitive dysfunctions particularly Alzheimer’s related disorders, have been discussed with special reference to their possible mechanism of action.

INTRODUCTION

The process of knowing, thinking, understanding, problem solving, judgment, processing of information regarding images, concepts, words, rules, symbols and creativity is termed as cognition. Cognition is that operation of mind by means of which, we become aware of our surroundings, objects and thoughts. Cognitive ability begins with perception, followed by gathering of information/acquisition, its storage and interpretation with the involvement of various sense organs so as to yield meaningful knowledge (pattern recognition for example) thereby adding to our experience (Fig. 1). Cognitive disorders such as delirium, dementia and amnesic disorders are common in elderly individuals (Fig. 2). The key features of these dreaded disorders are memory impairments, deterioration of language, visuospatial, motor, sensory abnormalities, gait disturbance and seizures. There are around 30 million patients suffering from Alzheimer’s disease (AD) which is the major cause of dementia, all over the world. In India, AD patents are estimated to be around 3 million. Presently, there are no satisfactory diagnostic procedures and therapeutic regimens available for the management of these cognitive disorders. Despite the severity and high prevalence of these diseases, Allopathic system of medicine is yet to provide a satisfactory remedy. Therefore, neurobiologists all over the world are looking for new directions and alternative strategies for managing cognitive disorders (Fig. 3). Dementia of the Alzheimer’s type 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. Nowadays, however, dementia is a very common illness in the elderly. According to the Alzheimer’s Association, AD is the most common cause of dementia in the elderly, i.e. approximately two-thirds of all cases of dementia. There are around 35 million patients suffering from Alzheimer’s disease all over the world, out of which United States of America
alone has around 4.5 million patients. AD is a neurodegenerative disorder affecting major brain areas including the cortex and limbic system, and is characterized by progressive decline in memory with impairment of at least one other cognitive function. AD often begins with symptoms like short-term memory loss, and continues with more widespread cognitive and emotional dysfunction. So-called late-onset AD (LOAD) occurs after age 65. AD features ongoing deterioration of patients’ functioning which results in substantial and long-lasting disability over the approximate 7-10 years from diagnosis to eventual death. Although AD usually shows no symptom on motor or sensory alterations, certain atypical clinical presentations (such as spastic paraparesis, Fig. 3) are occasionally found in some patients.

Various traditional approaches practiced in India for prevention and treatment of diseases so as to maintain/restore health include Ayurveda, yoga, unani, siddha, homeopathy, naturopathy and complimentary systems. Ayurvedic system is based on three fundamental principles or doshas called vata, pitta and kapha. These doshas govern all cellular processes responsible for healthy life. Vata governs all movements/activities, pitta governs heat/energy levels and regulates various transformations whereas, kapha controls growth, structural modifications and lubrication. When these principles, which guide the processes of our body/mind get disturbed in an individual due to bad environment or poor diet the individual starts suffering from some disease. For instance, when, vata gets out of balance, the consequences are hyperactive mind, circulatory disorders, poor neurotransmission, irregular elimination and uncomfortable menses. If pitta is disturbed, we observe excessive acidity resulting in heartburn, peptic ulcers, hot temper and inflammations. Whereas, if kapha gets out of balance, the result is chronic congestion, weight gain, high cholesterol levels and acne.

Nootropic agents such as piracetam, pramiracetam, aniracetam and cholinesterase inhibitors like Donepezil®, rivastigmine and galantamine are prescribed for improving memory and behavior. However, the resulting side effects associated with these agents have limited their use. Therefore, it is worthwhile to explore the utility of traditional medicines in the treatment of various cognitive disorders. Various traditional systems of medicines emphasize use of herbs, nutraceuticals or life style changes for controlling age related neurodegenerative disorders.

Dementia involves a profound deterioration in mental functioning characterized by several problems with memory and by one or more of cognitive deficits like aphasia, apraxia, agnosia and disturbance in executive functioning. There are more than 70 known causes of dementia, including brain diseases such as Alzheimer’s disease and Pick’s disease and infection or disorders that affect the functioning of the brain, such as meningitis, HIV infection and encephalitis (Fig. 4). In some cases, can be halted or reversed, especially when it is caused by certain types of tumors and treatable infections or when it results from depression or substance abuse. Most dementias are progressive and irreversible, however including the most common form, dementia of the Alzheimer’s type. Alzheimer’s disease accounts for more than half of the cases of dementia. Dementias usually occur in people over the age of 80. Those that begin after age 65 are called late-onset or senile dementias. Those that begin at age 65 or earlier are termed early-onset or presenile dementias.

Phytochemicals have long been recognized to possess many properties, including antioxidant, antiinflammatory, antiviral, antiproliferative, and anticarcinogenic. However, with respect to all health-promoting benefits, considerable interest over the past decades has primarily been focused on examining their roles in reducing risk factors associated with cancer and heart disease. Consequently, there still remains a paucity of studies that have investigated their role in brain functions such as learning and memory, decrements in which, as alluded to above, are likely to have a negative impact on the quality of life. Of those phyto-chemicals having been investigated, those most familiar to the general public are Chinese herbal remedies such as Ginkgo biloba (EGb 761) and ginseng. While continued research is being undertaken to further understand the biological actions of these extracts, the underlying beneficial effects of phytochemicals from other dietary sources such as fruits and vegetables, with respect to brain performance, are only beginning to receive increased attention. This review is directed towards familiarizing the reader with the available literature pertaining to the beneficial role(s) performed by phytochemicals in improving certain age-related neurological dysfunctions. Among therapeutic interventions that are envisioned to forestall or delay the normal and pathological aging processes, nutritional interventions may be viewed as a viable approach.

Polyphenolics

Polyphenolic compounds (flavonoids) occur ubiquitously in foods of plant origin, with over 4000 different structures having been identified and described. Although polyphenolic research has spanned several de-cades, it has recently intensified due to our increasing understanding of the potential beneficial effects that these compounds promote towards improving human health. However, all too often, a simplistic approach to the biological importance of the dietary antioxidants has been investigated. Many investigators appear to be satisfied by merely implying that an increase in antioxidant status following dietary consumption is sufficient evidence to suggest that there will be an overall benefit to biological systems and processes. While this may be true in part, corroboration of such claims with observable beneficial outcomes to validate the true beneficial potential that consumption of dietary antioxidants afford, in particular those pertaining to the brain, are lacking.

Fruits and vegetables

Investigations of the potential effects of fruit and vegetable components and cognitive functions have, until recently, been limited. Aged garlic extract (AGIE, Allium sativum), which contains S-allylcysteine, S-allymercaptocysteine, allicin, and diallosulfides, has been reported to exhibit beneficial...
effects towards cognitive impairments in a novel strain of senescence accelerated mouse (SAM) 16-19.

It has been opined that in addition to antioxidant activity, changes in the immune response may contribute to a number of age-related impairments in cognitive performance 20-21. In this regard, a recent study by Zhang and colleagues 16, found that thymectomized mice supplemented with AGlE displayed marked improvement in a number of markers of immune function. AGlE treatment was found to prevent the reduction of thymectomy-induced antibody production and improve thymectomy-induced deterioration of learning behaviors (performance in a passive avoidance and spatial memory task). Interestingly, both AGlE and a high molecular protein fraction of AGlE have been reported to increase oxidative burst in murine macrophages, and enhance T-lymphocyte [64] and human lymphocyte proliferation. Together this evidence would suggest that AGlE may exert some protective effects in SAM through immunomodulatory mechanisms, since it has been shown that unfavorable changes in the immune system result in impairment of learning and memory functions 20-21.

In addition to AGlE, red bell pepper (Capsicum annuum L.) has also been employed in the SAM model, and beneficial effects were observed in both memory and acquisition performance 22. Thus, to the extent that the SAM model is effective in aging, both garlic and red bell pepper may have positive benefits on age-related deficits.

**Tea**

While increased consumption of polyphenolics from tea has been found to correlate with reduced incidence of certain cancers 23-24, they have also been suggested to elicit potentially beneficial effects towards improving brain function(s). A study by Matsuoka and co-workers 25, found that intracisternal injection of epicatechin improved the memory impairment induced by intracisternal glucose oxidase, and iv injection of catechin or epicatechin improved deficits induced by the cerebral ischemia. One could argue that the protection afforded by tea polyphenolics against ischemic damage was due in part to inhibition of oxidative and inflammatory processes 26-28.

### Phytochemicals useful in Cognitive dysfunctions

<table>
<thead>
<tr>
<th>Phytochemical</th>
<th>Botanical source</th>
<th>Mechanism of action</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daidzein</td>
<td>Pueraria thunbergiana</td>
<td>ChAT activator</td>
<td>48.</td>
</tr>
<tr>
<td>Flavan-3-ol gallate esters:</td>
<td>Thea sinensis</td>
<td>Neuroprotective</td>
<td>49.</td>
</tr>
<tr>
<td>Epicatechin gallate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epigallocatechin gallate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallic acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetocide</td>
<td>Callicarpa dichotoma</td>
<td>Attenuate glutamate induced neurotoxicity</td>
<td>50.</td>
</tr>
<tr>
<td>Fleminginin</td>
<td>Flemingia macrophyla</td>
<td>Protect neuronal cells from Abeta-induced damage</td>
<td>51.</td>
</tr>
<tr>
<td>Flemingichromone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flemingichalcone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osajin, 5,7,4'-trihydroxy-6,8-diprenylisoflavone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,7,4'-trihydroxy-6,3'-diprenylisoflavone, Aureole Polyphenols</td>
<td>Vaccinium frondosum</td>
<td>Reverse age-related decline in neuronal signal transduction Neuroprotective</td>
<td>52.</td>
</tr>
<tr>
<td>Thomsonide</td>
<td>Punica granatum</td>
<td>Improve memory, registration</td>
<td>53.</td>
</tr>
<tr>
<td>Withanolides 1, 3, 4, 5</td>
<td>Puerariae flos</td>
<td>Cholinesterase inhibitor</td>
<td>54.</td>
</tr>
<tr>
<td>Siteindosides 8, 9, 10</td>
<td>Ajuga bracteosa</td>
<td>Cognitive enhancer</td>
<td>55.</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Withania somnifera</td>
<td>Anti-amyloid</td>
<td>56.</td>
</tr>
<tr>
<td>Cynatroside B</td>
<td>Curcuma longa</td>
<td>Antioxidant</td>
<td>57.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligonol</td>
<td>Viitis winifera</td>
<td>Attenuate Abeta-induced cytotoxicity</td>
<td>58.</td>
</tr>
<tr>
<td>Lycopodine</td>
<td>Lycopodium clavatum</td>
<td>AChE inhibitor</td>
<td>59.</td>
</tr>
<tr>
<td>Lycodine</td>
<td></td>
<td>Improve learning and memory</td>
<td></td>
</tr>
<tr>
<td>Fawcettimine, Huperzine A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polysacharides J, J3, and J4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bellidin, Bellidifolin, Bellidin 8-O-β-glucopyranoside</td>
<td>Nerium indicum</td>
<td>Neuroprotective</td>
<td>60.</td>
</tr>
<tr>
<td>Alaternin</td>
<td>Gentiana campestris</td>
<td>AChE inhibitor</td>
<td>61.</td>
</tr>
<tr>
<td>Nor-rubrofusarin glucose</td>
<td>Cassia tora</td>
<td>Inhibit peroxynitrite toxicity and nitration</td>
<td>62.</td>
</tr>
</tbody>
</table>
Baicalein  
*Scutellaria baicalensis*  
Reduce cytotoxicity of Abeta protein in PC12 cells  
Reduction of oxidative stress  

Galanthamine  
*Galanthus nivalis*  
Slow down neuronal degeneration  

Dihydro tanshinone  
*Salvia miltiorrhiza*  
AChE inhibitors  

Crypto tanshinone  
Tanshinone i, iia  

Cannabidiol  
*Cannabis sativa*  
Neuroprotective  
Antioxidant  
Antiapoptotic  

Naringenin  
*Citrus junoson*  
Neuro protective  

Cis-9-octadecenoamide (oleamide)  
*Lycopodium clavatum*  
AChE inhibitor  

A-onocerin  
*Bacopa monniera*  
Cognition enhancer  

Bacoside a & b  
Ginkgo biloba  
Increases cerebral glucose metabolism  
Improve memory  

Hyperforin  
*Hypericum perforatum*  
Improves cognition  

Deoxypeganine  
*Peganum harmala*  
AChE & monoamino oxidase inhibitor  

Huperzine  
*Huperiza serrata*  
AChE inhibitor  
Improves cognition  

Vinpocetine  
*Vinca alba*  
Improves blood flow to brain  

Reserveratrol  
*Vitis winifera*  
Inhibition of excitatory synaptic transmission, neuroprotective, Improves cognition  

[6]-gingerol  
*Zingiber officinale*  
Nootropic  

Piperine  
*Nootropic*  

Phyllanthin  
*Nootropic*  

Hyperforin:  
\(\text{R}_1\text{R}_2\text{R}_3\text{OH}\)  

Ginkgolide A:  
\(\text{OH}\text{H}\text{OH}\)  

Ginkgolide B:  
\(\text{OH}\text{OH}\text{H}\)  

Ginkgolide C:  
\(\text{OH}\text{OH}\text{OH}\)  

Ginkgolide J:  
\(\text{OH}\text{H}\text{OH}\)  

Ginkgolide M:  
\(\text{H}\text{OH}\text{OH}\)  

Galanthamine:  
\(\text{R}_1\text{R}_2\text{R}_3\text{OH}\)  

Curcumin:  
\(\text{R}_1\text{R}_2\text{R}_3\text{OH}\)  

Daizайн:  
\(\text{R}_1\text{R}_2\text{R}_3\text{OH}\)
Pharmacognosy Reviews
Vol 2, Issue 3, Jan-Jun, 2008

Carotenoids, vitamin E and vitamin C
Very few reports have actually investigated the effect(s) of dietary supplementation of vitamin E and C or carotenoids on age-related cognitive impairments. The majority of studies having identified their role(s) on brain functions have done so through dietary deficiency. Nonetheless, numerous epidemiological studies have reported some positive benefits of dietary carotenoids on age-related impairments in memory and learning performance. In parallel with these assessments, correlations with flavonoids and vitamins E and C have also been reported with mixed results. There is, however, growing evidence to suggest a potential beneficial effect of these compounds, in particular vitamin E, against the damaging effects of neurodegenerative disorders such as AD and PD 29.

Ginkgo biloba (EGb 761)
EGb 761 is a standardized extract of dried leaves of Ginkgo biloba. It has also been shown to be an effective free radical scavenger and a potent inhibitor of lipid peroxidation 30. As mentioned in the introduction, it is one of the most
extensively studied extracts with respect to cognitive performance in animal and human studies. A number of very good review articles have recently been published that are solely directed to dis-cussing Ginkgo and its various pharmacological actions, and the reader is referred to these for a comprehensive overview of the literature 32-34.

**Ginseng**

Panax ginseng is one of the mostly widely used herbs in traditional Chinese medicine. Currently, sales within the US amount to over $300 million annually. Some of the actions reported to be elicited by ginseng include an ability to induce effects within the CNS that control functions related to stamina, fatigue, and physical stress; and to modulate traditional Chinese medicine. Currently, sales within the US Ginseng for a comprehensive overview of the literature 32-34.

reported to be elicited by ginseng include an ability to induce effects within the CNS that control functions related to stamina, fatigue, and physical stress; and to modulate traditional Chinese medicine. Currently, sales within the US Ginseng for a comprehensive overview of the literature 32-34.
Bigl, Schilebs, Paul, Flechsig. Systemic administration of defined extracts from Chinese medicinal prescription, on long-term potentiation in the dentate gyrus in rats.


