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Potential of Phytochemicals in management of cognitive disorders- An Update

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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, fosracetam, 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 disorders1. 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

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alone has around 4.5 million patients 1. 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 2. 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 3. 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 4-5.

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. 6.

Nootropic agents such as piracetam, pramiracetam, aniracetam and cholinesterase inhibitors like Donepezil®, rivastigmine and galanthamine 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 7. Alzheimer's disease accounts for more then 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, antiallergic, anti-inflammatory, antiviral, antiproliferative, and anticarcinogenic 8-12. However, with respect to over 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 11. 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 in-creased 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 13. 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 11-15. 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 (AGlE, *Allium sativu*m), which contains S-allycisteine, S-allymercaptocysteine, allicin, and diallosulfides, has been reported to exhibit beneficial

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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 im-munomodulatory 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 an-nuum*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 intracis-ternal 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

Phytochemical	Botanical source	Mechanism of action	Ref.
Daidzein	*Pueraria thunbergiana*	ChAT activator	48.
Flavan-3-ol gallate esters: Epicatechin gallate Epigallocatechin gallate Gallic acid	*Thea sinensis*	Neuroprotective	49.
Acetocide	*Callicarpa dichotoma*	Attenuate glutamate induced neurotoxicity	50.
Flemінginin Flemingichromone Flemingichalcone Osajin, 5,7,4'-trihydroxy-6,8-diprenylisoflavone 5,7,4'-trihydroxy-6,3'-diprenylisoflavone, Aureole	*Flemingia macrophyla*	Protect neuronal cells from Abeta-induced damage	51.
Polyphenols	*Vaccinum frondosum*	Reverse age-related decline in neuronal signal transduction	52.
	Punica granatum	Neuroprotective	53.
Thomsonide	*Puerariae flos*	Improve memory, registration	54.
Withanolides 1, 3, 4, 5	*Ajuga bracteosa*	Cholinesterase inhibitor	55.
		Cognitive enhancer	56.
Sitoindosides 8, 9, 10	*Withania somnifera*		
Curcumin	*Curcuma longa*	Antiamyloid	57.
		Antioxidant	58.
Cynatroside B	*Cynanchum atratum*	Anti AChE	59.
		Antiamnesic	
Oligonol	*Vitis winifera*	Attenuate Abeta-induced cytotoxicity	60.
Lycopodine Lycodine Fawcettimine, Huperzine A	*Lycopodium clavatum*	AChE inhibitor Improve learning and memory	61.
Polysacharides J_2, J_3 and J_4	*Nerium indicum*	Neuroprotective	62.
Bellidin, Bellidifolin, Bellidin 8-O-β- glucopyranoside	*Gentiana campestris*	AChE inhibitor	63.
Alaternin Nor-rubrofusarin glucose	*Cassia tora*	Inhibit peroxynitrite toxicity and nitration	64.

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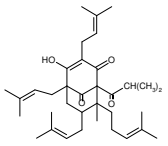
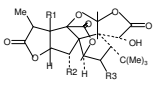
Baicalein Baicalin	*Scutellaria baicalensis*	Reduce cytotoxicity of Abeta protein in PC12 cells Reduction of oxidative stress	65.
Galanthamine	*Galanthus nivalis*	Slow down neuronal degeneration	66.
Dihydro tanshinone Crypto tanshinone Tanshinone i, iia	*Salvia miltiorhiza*	AChE inhibitors	67.
Cannabidiol	*Cannabis sativa*	Neuroprotective Antioxidant Antiapoptotic	68.
Naringenin	*Citrus junoson*	Neuro protective	69.
Cis-9-octadecenoamide (oleamide)	*Zizyphus jujuba*	Protects from scopolamine induced amnesia	70.
A-onocerin	*Lycopodium clavatum*	AChE inhibitor	71.
Bacoside a & b	*Bacopa monniera*	Cognition enhancer	72.
Ginkgolides	*Ginkgo biloba*	Increases cerebral glucose metabolism Improve memory	73.
Hyperforin	*Hypericum perforatum*	Improves cognition	74.
Deoxypeganine	*Peganum harmala*	AChE & monoamino oxidase inhibitor	75.
Huperzine	*Huperiza serrata*	AChE inhibitor Improves cognition	76, 77, 78.
Vinpocetine	*Vinca alba*	Improves blood flow to brain	79, 80.
Reserveratrol	*Vitis winifera*	Inhibition of excitatory synaptic transmission, neuroprotective, Improves cognition	81, 82, 83.
[6]-gingerol	*Zingiber officinale*	Nootropic	84.
Piperine	*Piper nigrum*	Nootropic	85.
Phyllanthin	*Phyllanthus Niruri*	Nootropic	86.



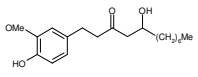
Hyperforin

(1S,5S,7S,8R)-4-hydroxy-8-methyl-3,5,7-triS (3-methylbut-2-enyl)
-8-(4-methylpent-3-enyl)-1-(2-methyl propanoyl) bicyclo [3,3,1] non-3-ene-2,9-dione.



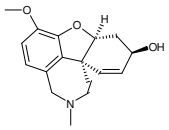
Ginkgolide

	R1 R1	R2 R2	R3 R3
Ginkgolide A:	OH	H	H
Ginkgolide B:	OH	OH	H
Ginkgolide C:	OH	OH	OH
Ginkgolide J:	OH	H	OH
Ginkgolide M:	H	OH	OH



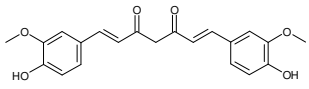
[6]-Gingerol

(5)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone.



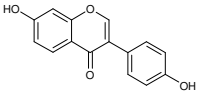
Galanthamine

(4aS, 6R, 8aS)-5,6,9,10,11,12-hyxahydro-3-methoxy-11-methyl)-4a4-(1)
benzofuro[3a,3,2-el] [2] benzazepin-6-01



Curcumin

(1E,6E)-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione.



Daidzein

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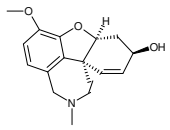
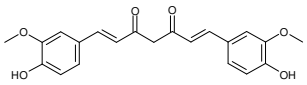


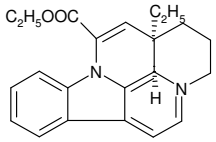
Galanthamine

(4aS, 6R, 8aS)-5,6,9,10,11,12-hyxahydro-3-methoxy-11-methyl)-4a4-(1) benzofuro[3a,3,2-el] [2] benzazepin-6-01



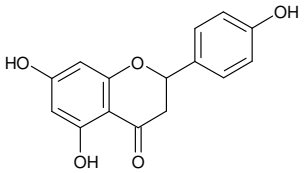
Curcumin

(1E,6E)-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione.



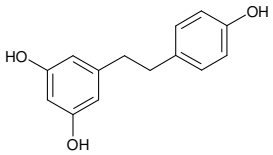
Vinpocetine

(3α,16α)-Eburamenine-14-carboxylic acid

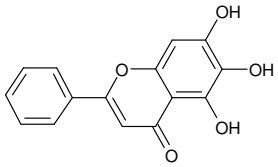


Naringenin

4',5,7-Trihydroxyflavanone

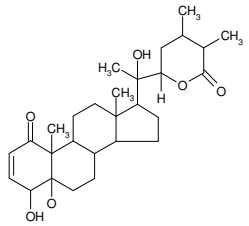


Trans-3,4,5-trihydroxystilbene

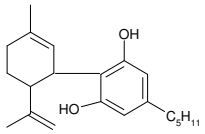


Baicalein

5,6,7-Trihydroxy flavone

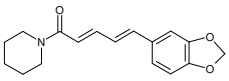


Withanolide - D



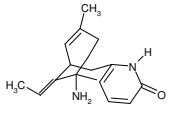
Cannabidiol

2-((1s,6s)-3-methyl-6-(prop-1-en-2-yl)cyclohexa-2-enyl)-5-pentylbenzine-1,3-diol.



Piperine

1-(5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadenyl piperidine.



Huperzine A

5,9-Methanocycloocta[b]pyridine-2(1H)-one

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

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extensively studied extracts with respect to cognitive performance in animal and human studies 31. 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 immune function and functions such as memory, learning, and behavior 35. A number of different cognitive tests have shown the potential bene-ficial effects of ginseng on memory and learning in performance in a variety of animal species 36-39. In addition, herbal mixtures that contain ginseng have been shown to improve cognitive performance. These include S-113m 40-41, which consists of *Biota ori-entalis*, *Panax ginseng*, and *Schizandra chinesis* (1:1:3 w/w/w), and DX-9386 42-46, which consists of *Panax ginseng*, *Polygala tenuifol*a, *Acorus gramineus*, and *Paoria cocos* (1:1:25:50 w/w, dry). It has been suggested that one potential mechanism by which ginseng improves various neurological functions is through an interaction with the cholinergic and sero-toninergic neurotransmitter systems 47.

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