



American Journal of **Food Technology**

ISSN 1557-4571



Academic
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Effect of some Plants and Pesticides on Acetylcholinesterase

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ABSTRACT

The principal role of acetylcholinesterase (AChE) is the termination of nerve impulse transmission at the cholinergic synapses by rapid hydrolysis of acetylcholine (ACh). Inhibition of AChE serves as a strategy for the treatment of Alzheimer's Disease (AD). Several acetylcholinesterase inhibitors (AChEIs) are used for the symptomatic treatment of AD. A potential source of AChE inhibitors is certainly provided by the abundance of plants in nature. The aim of this article is to study the effect of some plants and pesticides on acetylcholinesterase. Several plants considered as a source of acetylcholinesterase inhibitors and pesticides special organophosphorus.

Key words: Acetylcholinesterase inhibitor, plant extracts, pesticides, Alzheimer's disease

INTRODUCTION

Cholinesterase inhibitors are the only approved drugs for treating patients with mild to moderately severe Alzheimer's disease, a disorder associated with progressive degeneration of memory and cognitive function. The memory impairment in patients with Alzheimer's disease results from a deficit of cholinergic function in the brain. The most important changes observed in the brain are a decrease in cortical levels of the neurotransmitter acetylcholine and associated enzyme choline transferases. Acetylcholinesterase inhibitors can restore the level of acetylcholine by inhibiting acetylcholinesterase. Principal role of acetylcholinesterase (AChE) is the termination of nerve impulse transmission at the cholinergic synapses by rapid hydrolysis of acetylcholine (ACh). Inhibition of AChE serves as a strategy for the treatment of Alzheimer's Disease (AD), senile dementia, ataxia, myasthenia gravis and Parkinson's disease (Kumar *et al.*, 2011). There are a few synthetic medicines, e.g., tacrine, donepezil and the natural product-based rivastigmine for treatment of cognitive dysfunction and memory loss associated with AD.

There are two types of cholinesterase, AChE and butyrylcholinesterase (BuChE). The AChE is found primarily in the blood and neural synapses. The BuChE is found primarily in the liver. The biggest difference between the two is the substrates. The AChE hydrolyzes acetylcholine (ACh) more quickly and BuChE hydrolyzes butyrylcholine (BuCh) more quickly. The BuCh is a synthetic compound used to distinguish AChE receptors from BuChE receptors. Many of the drugs that are available for treatment of AD target both AChE and BuChE but some are more (Mehta *et al.*, 2012). These compounds have been reported to have their adverse effects including gastrointestinal disturbances and problems associated with bioavailability, which necessitates the interest in finding better AChE inhibitors from natural resources. In traditional practices numerous plants have been used to treat cognitive disorders, including neurodegenerative diseases and different neuron pharmacological disorders.

Hence, an effort has been made to establish the scientific validity to investigate and screening for acetyl cholinesterase inhibitory activity of methanolic extract of cassia fistula roots. The result suggests that the AChE inhibitors should be alkaloids and these typical insole alkaloids have not been studied for their AChE activity before. Rajasree *et al.* (2012) proved that the roots of cassia fistula plant can be used for the isolation of acetylcholinesterase inhibitors, which are widely used in the treatment of Alzheimer's disease.

ACETYL CHOLINESTERASE INHIBITORS FROM PLANTS

Mukherjee *et al.* (2007) provide a comprehensive literature survey of plants that have been tested for AChE inhibitory activity as shown in Table 1.

ACETYLCHOLINESTERASE INHIBITION BY SOME PROMISING BRAZILIAN MEDICINAL PLANTS

Based on the cholinergic hypothesis, acetylcholinesterase inhibitors (AChEIs) are widely used to treat Alzheimer's disease (Francis *et al.*, 1999). Galanthamine, an alkaloid from plants of the Amaryllidaceae family, is a selective reversible long-acting and competitive acetyl cholinesterase inhibitor (AChEI). This compound is considered to be more effective in the treatment of Alzheimer's Disease (AD) and have fewer limitations than physostigmine and tacrine (Wilcock *et al.*, 2000). Many plants have been reported as interesting sources of AChEI (Gupta and Gupta, 1997; Mukherjee *et al.*, 2007).

The synthetic drug tacrine (Cognex) was the first AChEI to be licensed, but its routine use has been largely restricted due to its hepatotoxicity. Thus, plants that have demonstrated hepatoprotective activity are relevant in terms of searching for novel formulations or compounds for AD treatment.

Plants that have shown favorable effects in relation to cognitive disorders, including anticholinesterase, anti-inflammatory and antioxidant activities or other relevant pharmacological activities are potentially of interest for clinical use for AD. Plants which affect the cholinergic function in the Central Nervous System (CNS) are particularly relevant in treating AD (Howes and Houghton, 2003). Besides being used as a medicine; AChEIs are a widely used class of insecticides (Finkelstein *et al.*, 2002).

In order to discover novel potential sources for AChEIs, a microplate assay and a TLC assay were used to screen/for AChE inhibitory activity in ethyl acetate and methanol extracts from Brazilian medicinal plants (Ellman *et al.*, 1961; Rhee *et al.*, 2001; Ingkaninan *et al.*, 2003). Eighteen species were screened and the results show that several plants are very interesting candidates for further isolation of AChEIs.

INHIBITION OF ACETYLCHOLINESTERASE (AChE) BY PESTICIDES

The large amount of pesticide residues in the environment is a threat to global health by inhibition of acetylcholinesterase (AChE). Biosensors for inhibition of AChE have been thus developed for the detection of pesticides. In line with the rapid development of nanotechnology, nanomaterials have attracted great attention and have been intensively studied in biological analysis due to their unique chemical, physical and size properties (Xia *et al.*, 2015).

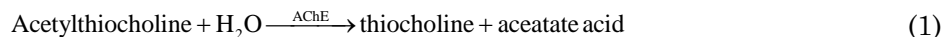
The AChE-based sensing systems include the use of AChE alone or combination with cholineoxidase (ChO). The AChE inhibition in the single and bienzyme systems is monitored by determining the generated enzyme production. The AChE can hydrolyze acetylcholine or acetylthiocholine (a synthesized analogues of acetylcholine) to produce choline or thiocholine

Table 1: Plants with acetylcholinesterase inhibitory activity

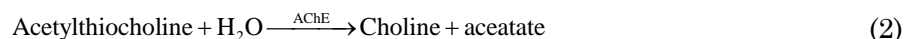
Plants	Family	Parts used	Types of extract	Activity		References
				Inhibition (%)	Concentration (mg mL ⁻¹)	
<i>Abutilon indicum</i> Linn.	Malvaceae	Whole	Methanolic	30.667	1.06 (0.1)	Ingkaninan <i>et al.</i> (2003)
<i>Acanthus ebracteatus</i> Vahl.	Acanthaceae	Aerial part	Methanolic	36.197	8.00 (0.1)	Ingkaninan <i>et al.</i> (2003)
<i>Aegle marmelos</i> (Linn.) Correa ex Roxb.	Rutaceae	Fruit pulp	Methanolic	44.657	3.04 (0.1)	Ingkaninan <i>et al.</i> (2003)
<i>Albizia procera</i> (Roxb.) Benth	Leguminosae	Bark	Methanolic	40.717	0.46 (0.1)	Ingkaninan <i>et al.</i> (2003)
<i>Baxopa monniera</i> Linn.	Scrophulariaceae	Whole	Ethanol	42.097	1.02 (0.1)	Das <i>et al.</i> (2002)
<i>Butea superba</i> Roxb.	Leguminosae	Root barks	Methanolic	55.877	5.83 (0.1)	Ingkaninan <i>et al.</i> (2003)
<i>Buxus sempervirens</i> Linn.	Buxaceae	Whole	Chloroform: methanol (1:1)	61.767	0.76 (1)	Orhan <i>et al.</i> (2004)
<i>Carthamus tinctorius</i> Linn.	Compositae	Flower	Methanolic	30.337	9.22 (0.1)	Ingkaninan <i>et al.</i> (2003)
<i>Cassia fistula</i> Linn.	Leguminosae	Roots	Methanolic	54.137	3.90 (0.1)	Ingkaninan <i>et al.</i> (2003)
<i>Corydalis solida</i> Linn.	Papaveraceae	Whole	Chloroform: methanol (1:1)	87.567	1.24 (1)	Orhan <i>et al.</i> (2004)
<i>Cyperus rotundus</i> Linn.	Cyperaceae	Whole	Methanolic	44.197	2.27 (0.1)	Ingkaninan <i>et al.</i> (2003)
<i>Euphorbia antiquorum</i> Linn.	Euphorbiaceae	Stem	Methanolic	42.317	9.10 (0.1)	Ingkaninan <i>et al.</i> (2003)
<i>Fumaria vaillantii</i> Lois.	Fumariaceae	Whole	Chloroform: methanol (1:1)	94.237	0.47 (1)	Orhan <i>et al.</i> (2004)
<i>Fumaria capreolata</i> Linn.	Fumariaceae	Whole	Chloroform: methanol (1:1)	96.897	0.17 (1)	Orhan <i>et al.</i> (2004)
<i>Fumaria kralikii</i> Jordan	Fumariaceae	Whole	Chloroform: methanol (1:1)	84.987	1.07 (1)	Orhan <i>et al.</i> (2004)
<i>Fumaria asepalata</i> Boiss.	Fumariaceae	Whole	Chloroform: methanol (1:1)	91.997	0.70 (1)	Orhan <i>et al.</i> (2004)
<i>Fumaria densiflora</i> DC.	Fumariaceae	Whole	Chloroform: methanol (1:1)	93.427	0.92 (1)	Orhan <i>et al.</i> (2004)
<i>Fumaria flabellata</i> Linn.	Fumariaceae	Whole	Chloroform: methanol (1:1)	92.147	1.01 (1)	Orhan <i>et al.</i> (2004)
<i>Fumaria petteri</i> Reichb subsp.	Fumariaceae	Whole	Chloroform: methanol (1:1)	89.457	0.86 (1)	Orhan <i>et al.</i> (2004)
<i>Thuretii</i> (Boiss.)						
<i>Fumaria macrocarpa</i> Boiss. ex Hausskn	Fumariaceae	Whole	Chloroform: methanol (1:1)	93.437	0.64 (1)	Orhan <i>et al.</i> (2004)
<i>Fumaria cilicica</i> Hausskn	Fumariaceae	Whole	Chloroform: methanol (1:1)	88.037	0.65 (1)	Orhan <i>et al.</i> (2004)
<i>Fumaria parviflora</i> Lam.	Fumariaceae	Whole	Chloroform: methanol (1:1)	87.027	0.31 (1)	Orhan <i>et al.</i> (2004)
<i>Fumaria judaica</i> Boiss.	Fumariaceae	Whole	Chloroform: methanol (1:1)	96.477	0.63 (1)	Orhan <i>et al.</i> (2004)

Source: Mukherjee *et al.* (2007)

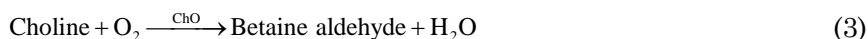
(a thiol compound), respectively. In the single enzyme system, AChE hydrolyzes acetylthiocholine to produce the thiocholine (Eq. 1):



In the bienzyme system, AChE catalyzes the hydrolysis of acetylcholine into acetate and choline (Eq. 2):



The choline is subsequently converted by ChO, producing hydrogen peroxide in the presence of oxygen (Eq. 3):



Traditional optical methods to measure the levels of AChE and its inhibitors include the spectrophotometric thiol assay by using Ellman's reagent and the colorimetric detection of H_2O_2 produced by oxidation of the AChE-induced choline by using horseradish peroxidase (HRP) (Pohanka *et al.*, 2009; Rhouati *et al.*, 2010). However, the methods lack sufficient sensitivity and require time-consuming sample-handling procedures. In order to enhance the detection sensitivity, advanced techniques based on metallic/magnetic nanoparticles and quantum dots have been developed recently, including colorimetric and fluorescent assays and surface plasmon resonance. Their preparation, modification and detection principle are presented in Fig. 1.

Pesticides are used in modern agricultural procedures to achieve the high production level and quality of field crops. Many of these pesticides were used in controlling cattle insecticides particularly flies, lice and grubs. Man's food can serve as a continual in the human body. The WHO/FAO and FDA have monitored the level of pesticides in raw and processed foods. A part of this study since 1963 was reported by Duggan and Dawson (1987). The data indicated that the average U.S. diet contained the following residues: chlorinated organic chemical 0.02 ppm, organophosphate 0.003 ppm, carbonate 0.05 ppm.

In USA and Europe, intensive efforts and research however, have been given to the removal as reduction of residues on raw milk and dairy products. Abd Rabo *et al.* (1980) studied the effect of heat treatments on pesticide residues in buffalo's milk.

They found that sterilization of milk is the most effective heat treatment which remove or reduce the concentration of pesticide residues followed by boiling and finally pasteurization.

Manufacture of novel functional beverages with antioxidant and anti-acetylcholinesterase activities.

Nowadays, there is increased consumer demand for high-antioxidant foods. Drinking high-antioxidant beverages may help to protect against aging. Alzheimer's disease and other chronic diseases. Grapes and some plants including *Phyllanthus emblica*, *Terminally chebula*, *Kaempferia parviflora*, *Centella asiatica*, *Nelumbo nucifera*, *Rauwolfia serpentina*, *Ginkgo biloba*, *Crocus sativus*, *Clitoris ternatea* and others are well-known to possess antioxidant, neuroprotective and other health-promoting activities. Thus, it is possible to use these plants for the development of new functional beverages.

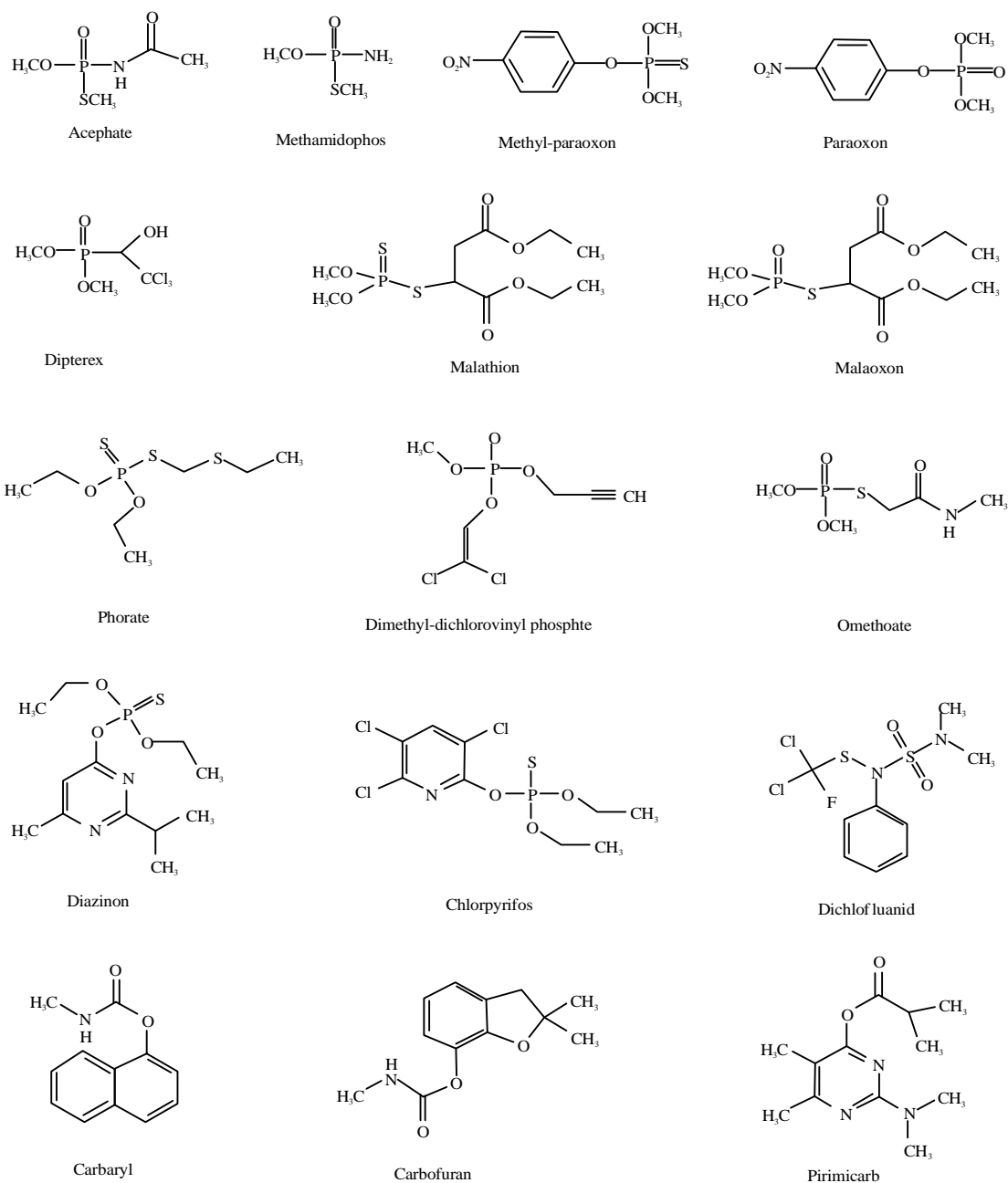


Fig. 1: Structures of the main pesticides used as target in AChE-based biosensors

Nanasombat *et al.* (2015) manufactured functional beverages with antioxidant and anti-acetylcholinesterase activities. They prepared ten formulations of beverages contained dried medicinal plants, fresh grapes and others. They found that the resultant beverages contained valuable sources of natural antioxidants and acetylcholinesterase inhibitors and may provide health benefits when consumed specially the beverage which contained 0.62% A-polycephala fruits, 0.35% *C. ternatea* flowers, 0.44% *G. biloba* leaves, 2.64% *K. parviflora* rhizomes, 1.76% *P. emblica* fruits, 0.88% *T. chebula* fruits, 5.28% brown sugar and 88.03% water.

CONCLUSION

Various plants are very interesting for further isolation of acetyl cholinesterase inhibitors, which are widely used in treatment of Al Zheimer's disease.

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