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 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 affective 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 AChE (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.
| Plants                        | Family       | Parts used | Types of extract | Inhibition (%) | Concentration (mg mL\(^{-1}\)) | References                  |
|------------------------------|--------------|------------|------------------|----------------|---------------------------------|-----------------------------|
| *Abutilon indicum* Linn.     | Malvaceae    | Whole      | Methanolic       | 30.667         | 1.06 (0.1)                      | Ingkaninan et al. (2003)    |
| *Acanthus ebracteatus* Vahl. | Acanthaceae  | Aerial part| Methanolic       | 36.197         | 8.00 (0.1)                      | Ingkaninan et al. (2003)    |
| *Aegle marmelos* (Linn.) Correa ex Roxb. | Rutaceae  | Fruit pulp | Methanolic       | 44.657         | 3.04 (0.1)                      | Ingkaninan et al. (2003)    |
| *Albizia procera* (Roxb.) Benth | Leguminosae | Bark       | Methanolic       | 40.717         | 0.46 (0.1)                      | Ingkaninan et al. (2003)    |
| *Bazopa monniera* Linn.      | Scrophulariaceae | Whole  | Ethanolic        | 42.097         | 1.02 (0.1)                      | Das et al. (2002)           |
| *Butea superba* Roxb.        | Leguminosae  | Root barks | Methanolic     | 55.877         | 5.83 (0.1)                      | Ingkaninan et al. (2003)    |
| *Buxus sempervirens* Linn.   | Buxaceae     | Whole      | Chloroform: methanol (1:1) | 61.767         | 0.76 (1)                         | Orhan et al. (2004)         |
| *Carthamus tinctorius* Linn. | Compositae   | Flower     | Methanolic       | 30.337         | 9.22 (0.1)                      | Ingkaninan et al. (2003)    |
| *Cassia fistula* Linn.       | Leguminosae  | Roots      | Methanolic       | 54.137         | 3.90 (0.1)                      | Ingkaninan et al. (2003)    |
| *Corydalis solida* Linn.     | Papaveraceae | Whole      | Chloroform: methanol (1:1) | 87.567         | 1.24 (1)                         | Orhan et al. (2004)         |
| *Cyperus rotundus* Linn.     | Cyperaceae   | Whole      | Methanolic       | 44.197         | 2.27 (0.1)                      | Ingkaninan et al. (2003)    |
| *Euphorbia antiquorum* Linn. | Euphorbiaceae| Stem       | Methanolic       | 42.317         | 9.10 (0.1)                      | Ingkaninan et al. (2003)    |
| *Fumaria vaillantii* Lois.   | Fumariaceae  | Whole      | Chloroform: methanol (1:1) | 94.237         | 0.47 (1)                         | Orhan et al. (2004)         |
| *Fumaria capreolata* Linn.   | Fumariaceae  | Whole      | Chloroform: methanol (1:1) | 96.897         | 0.17 (1)                         | Orhan et al. (2004)         |
| *Fumaria kraliihi* Jordan     | Fumariaceae  | Whole      | Chloroform: methanol (1:1) | 84.987         | 1.07 (1)                         | Orhan et al. (2004)         |
| *Fumaria asepala* Boiss.     | Fumariaceae  | Whole      | Chloroform: methanol (1:1) | 91.997         | 0.70 (1)                         | Orhan et al. (2004)         |
| *Fumaria densiflora* DC.     | Fumariaceae  | Whole      | Chloroform: methanol (1:1) | 95.427         | 0.92 (1)                         | Orhan et al. (2004)         |
| *Fumaria flabellata* Linn.   | Fumariaceae  | Whole      | Chloroform: methanol (1:1) | 92.147         | 1.01 (1)                         | Orhan et al. (2004)         |
| *Fumaria petteri* Reichb. subsp. | Fumariaceae | Whole  | Chloroform: methanol (1:1) | 89.457         | 0.98 (1)                         | Orhan et al. (2004)         |
| *Thuretii* (Boiss.)          | Fumariaceae  | Whole      | Chloroform: methanol (1:1) | 93.437         | 0.64 (1)                         | Orhan et al. (2004)         |
| *Fumaria macrocarpa* Boiss. ex Haussk. | Fumariaceae | Whole  | Chloroform: methanol (1:1) | 88.037         | 0.65 (1)                         | Orhan et al. (2004)         |
| *Fumaria ciclícica* Haussk.  | Fumariaceae  | Whole      | Chloroform: methanol (1:1) | 87.027         | 0.31 (1)                         | Orhan et al. (2004)         |
| *Fumaria parviflora* Lam.    | Fumariaceae  | Whole      | Chloroform: methanol (1:1) | 96.477         | 0.63 (1)                         | Orhan et al. (2004)         |

Source: Mukherjee et al. (2007)
(a thiol compound), respectively. In the single enzyme system, AChE hydrolyzes acetylthiocholine to produce the thiocholine (Eq. 1):

\[
\text{Acetylthiocholine} + \text{H}_2\text{O} \xrightarrow{\text{AChE}} \text{thiocholine} + \text{acetate acid}
\]  

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

\[
\text{Acetylthiocholine} + \text{H}_2\text{O} \xrightarrow{\text{AChE}} \text{Choline} + \text{acetate}
\]  

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

\[
\text{Choline} + \text{O}_2 \xrightarrow{\text{ChO}} \text{Betaine aldehyde} + \text{H}_2\text{O}
\]  

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 \(\text{H}_2\text{O}_2\) 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 \textit{Phyllanthus emblica}, \textit{Terminalia chebula}, \textit{Kaempferia parviflora}, \textit{Centella asiatica}, \textit{Nelumbo nucifera}, \textit{Rauwolfia serpentina}, \textit{Ginkgo biloba}, \textit{Crocus sativus}, \textit{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.
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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