Curing Incurable Alzheimer's Disease with Medicinal Plants [*]

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Abstract

Up to the present, Alzheimer's disease (AD), a dementia, is believed to be incurable; even its cause has not been documented. A few hypotheses have been postulated, however; among these are the destruction of acetylcholine by the enzyme acetylcholine-esterase, the accumulation of amyloid beta plaque, and peroxidation of the brain cells.

Since the disease was unknown in the olden days in Thailand, traditional Thai medicine pharmacopoeia did not include any therapy. This has encouraged a few Thai scientists to study a number of Thai medicinal plants (MPs) for curing AD. These are: (1) coconut – Cocos nucifera, *Arecaceae, whose water of young coconut contains phytoestrogen that mitigates the symptoms of AD of infected mice; (2) gardenia* – Gardenia augusta, *Rubiaceae, whose root extract counteracts acetylcholinesterase and amyloid beta plaque formation; (3) snowflake* – Wrightia antidysentarica, *Apocynaceae, whose stem extract inhibits the action of acetylcholinesterase; (4) 'Phrommi'* – Bacopa monnieri, *Schrophurariaceae, whose plant extract – bacoside – prolongs the symptoms of AD, (5) pepper* – Piper nigrum, *Piperaceae, whose black seed extract helps to recover AD of experimental animals; (6) 'Kwao Khruea Khao'* – Pueraria mirifica, *Papilio-noideae, whose root extract reduces the death of brain cells; and (7) 'Chan Chamot'* – Aglaia silvestris, *Meliaceae, whose plant extract - coumarin - inhibits acetylcholinesterase.*

In addition to the MPs studied by the Thai scientists, there are a few other MPs that were found to improve the symptoms of AD by other scientists. These are: (1) coconut oil that was found to produce ketone that substitutes glucose of the brain cells, thus improving the symptoms of AD; (2) turmeric – Curcuma longa, *Zingiberaceae, whose rhizome extract prevents peroxidation of the brain cells as well as destroying amyloid beta plaque; (3) Chinese clubmoss* – Huperzia serrata, *Lycopodiaceae, whose plant extract – huperzine A – inhibits the action of acetylcholinesterase; (4) snowdrop* – Galanthus nivalis, *Amaryllidiaceae, whose bulb alkaloid extract – galantamine – inhibits the action of acetylcholinesterase; and (5) tea* – Camellia sinensis, *Theaceae, whose green leaf extract inhibits the action of acetylcholinesterase as well as destroying amyloid beta plaque.*

Keywords: *Acetylcholinesterase, amyloid beta, coconut, gardenia, snowflake, tea pepper, 'Kwao Khreua Khao', 'Chan Chamot', turmeric, Chinese clubmoss, snowdrop.*

1. Introduction

With the increasing proportion of elderly people, the incidence of Alzheimer's disease (AD) is increasing every year. The use of medicinal plants (MPs) as an alternative prevention of the AD is of interest to many plant scientists. This article reviews the research results on MPs that have potential for the treatment of AD.

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2. The Role of Medicinal Plants in the Treatment of Alzheimer's Disease

Only recently that medicinal plants (MPs) started to play a role in the treatment of Alzheimer's disease (AD) since the disease was known only about a hundred years ago. As the disease is incurable even up to the present, several attempts have been made to investigate whether or not MPs can be used to treat the symptoms of AD. Among the role of MPs in treating AD are the following:

2.1 As MPs to Cure AD Directly

Normally, MPs used in curing a particular disease are quite safe for the users because by having low concentration they are quite safe for the users. MPs also have many active ingredients, each having synergistic effect with the others, they have a quite high efficiency in curing the disease. In addition, as MPs have been used for such a long time, if any was found to have harmful effect, they would have been abandoned a long time ago.

It was noted some time ago that consuming Asiatic pennywort (*Centella asiatica*) results in better concentration of the mind with good memory. This may be due to the effect of active ingredient in the leaf of this MP that helps in the eradication of toxic substances in the brain and the nervous system. Thus, Thai pharmacopoeia recommends the use of Asiatic pennywort to treat dementia.

In the case of AD, being a new emerging disease which our Thai ancestors have never encountered before, there is no Thai herbal medicine practitioner using an MP to cure it, and up to the present, there is no MP that has received acceptable proof among Thai MP practitioners to use it to treat AD. Thus, we have to wait for new research findings of any MPs that have active ingredients to cure AD, which is to be elaborated in the next sections.

2.2 As a Component of Modern Drug

Many modern drugs used to cure AD are derived from MPs, such as Reminyl, whose active ingredient - galantamine - is derived from snow drop, an MP of Eastern Europe. However, modern drugs, even though derived from MPS, still possess some drawbacks as they have side effects such as nausea, vomit, diarrhea. Moreover, these drugs are quite expensive. Thus, there is a need for research to find new drugs which are safe and with no side effects as well as reasonably priced.

3. Research on Using Thai MPs for the Treatment of AD

During the past few years, a number of Thai scientists have conducted research on Thai MPs for the treatment of AD. These are:

3.1 Coconut *(Cocos nucifera,* Family Araceae)

Dr. Nisaudah Radenahmad of the Department of Anatomy, Prince of Songkla University in Songkhla, Thailand, reported that young coconut water has a high concentration of a hormone – estrogen - which helps to delay the onset of AD (Chomchalow 2011). Her experiment on removing both ovaries of white mice, as a model of women with menopause that are deficient in estrogen, revealed that the mice that received the coconut water have less pathological symptoms than the ones that did not receive it. It is stated in her recent study that young coconut water could significantly reverse some pathologies associated with Alzheimer's disease (Radenahmad *et al*. 2011).

3.2 Gardenia *(Gardenia augusta,* Family Rubuiaceae)

Dr. Onrawee Kongsombat, Head of the Department of Physiology, Faculty of Medical Sciences, Naresuan University, conducted research on the effect of root extract of gardenia, in which previous studies have found that alcoholic extract of gardenia root has good *in vitro* antagonistic effect on the formation of acetylcholinesterase, which is an enzyme believed to digest acetylecholine – the neurotransmitter playing a vital role on the nervous system related to cognitive learning and memory. Inhibition of such enzyme results in prolonging the life of the neurotransmitter, making better the efficiency of learning and memory.

Such experiments were also extended to animal experiments. It was found that this gardenia root extract could inhibit the action of said enzyme as well as countering the reaction that damages the membranes of the brain cells

of the experimental animals. In studying behaviors in learning and memory, it was found that gardenia root extract could prevent the loss of memory caused by amyloid beta – a chemical responsible for destroying nervous cells. In studying the change in the structure of the cells, it was found that gardenia root extract could prevent the death of the nervous cells of the hippocampus, which is the part of the brain playing a vital role in building memory.

3.3 Snowflake *(Wrightia antidysenarica,* Family Apocynaceae)

Dr. Siriporn Chattipakorn, an instructor of the Department of Odontology and Oral Pathology, Faculty of Dentistry, Chiang Mai University, and also from the Cardiac Electrophysiology Research and Training Center, Physiology Department, Faculty of Medicine, Chiang Mai University, studied the effect of plant extract of snowflake on inhibitory effect of acetylcholinesterase in the brain. It was concluded that the enzyme of the extract was quite effective, particularly on the cerebral cortex, a part in the brain that plays a vital role in learning and memory. Such an enzyme destroys acetylcholine, the neurotransmitter of the nervous cells, which, upon decreasing, could cause AD (Chattipakorn *et al*. 2007). In addition, it also caused an increase in the activity of the nervous system in the brain of white rats; it also had a role in controlling the activity of neurotransmitting among nervous cells, the same as the action of galantamine, whose trade name is Reminyl.

3.4 Turmeric *(Curcuma longa,* Family Zingiberaceae)

Curcumin is an antioxidant that prevents oxidation; thus it is able to prevent peroxidation of the brain cells, which is a cause of AD. In addition, it was also found that curcumin could destroy amyloid beta and amyloid plaque in the AD patients, thus improving the symptoms of AD significantly (Fiala *et al*. 2007).

A researcher at Duke University in North Carolina in the US did an experiment providing a meal with turmeric curry or food cooked with curry powder, once or twice every week. It was found that such a meal could prevent AD symptoms. The researcher (Doraiswamy 2009) explained that curcumin in the curry has a vital role in preventing the distribution of amyloid beta in the brain, believed to be the cause of dementia. The American Alzheimer's Association has supported this research by providing the idea that the Indians who consume curry regularly have surprisingly low incidence of AD (Martin 2004).

3.5 'Phrommi' *(Bacopa monnieri,* Family Scrophurariaceae)

Dr. Kornkanok Ingkaninan, Head of the Center for Medicinal Plant Technology, Pharmaceutical Chemistry and Pharmacognosy Department, Faculty of Pharmacology, Naresuan University, and her colleagues have tested the chemical extract, named 'bacopaside' found in the 'Phrommi' plant, for its effect in increasing the learning and the memory and improving the brain's function of old-age persons with memory problems. It was found that this extract could delay the deterioration of the brain, could stimulate the memory, and could prevent the destruction of the brain cells and old-age persons from AD (Boontheuan 2009).

By consuming 'Phrommi' extract at the rate of 300 and 600 mg per day for three months, it was found that it could increase the efficiency in stabilizing the body, increasing the response to stimulants, increasing the capability to learn and memorize, relaxing depression, and no toxin and side effect were observed.

3.6 Pepper *(Piper nigrum,* Family Piperaceae)

Dr. Arunsri Sunthornpit and Dr. Srisomporn Preeprame, Faculty of Pharmaceutical Sciences, and Dr. Somdet Kanokmethakul, Faculty of Science, Khon Kaen University, extracted black pepper seeds for use in treating dementia. Two full years of the study were employed: in the first stage, the Faculty of Medicine has studied many MPs, such as onion bulb, Asiatic pennywort leaf, ginger rhizome, pepper seed, to see which one is the best. It was found that black pepper has a substance called piperine, which could revive the damaged brain portions. Further on, Chonpathompikunlert *et al*. (2010) stated that piperine, the main alkaloid of Thai black

pepper, protects against neurodegeneration and cognitive impairment in animal model of cognitive deficit like condition of AD.

3.7 'Kwao Khruea Khao' *(Peuraria mirifica,* Family Papiolionoideae)

Dr. Sayan Sawadsri, Department of Obstetrics and Gynecology, Mongkut Klao Medical College, Mongkut Klao Hospital, and his colleagues, in a cooperation among medical doctors of Mongkut Klao Hospital, Faculty of Eastern Medicine, Rangsit University, and the Emory University School of Medicine, conducted *in vitro* trial to find the preliminary benefits of 'Kwao Khruea Khao', whether or not it could inhibit the damage of the brain cells, including the promotion of the brain cells to grow and develop successfully. In the trial, a model was made to make the brain cells injured or malfunction, using three methods, namely: the oxidation, the burning of energy and the introduction of toxin into the body, brought about by consumption of food contaminated with chemicals, and toxic substances in the air. Then, 'Kwao Khreua Khao' extract was put in. It was found that the rate of death of the brain cells decreased by 30-40%, which is considered satisfactory, but an earlier statement (Anon. 2001) that "it would take some time to be certain that Kwao Khruea Khao could be used to treat AD" is still valid.

3.8 'Chan Chamot' *(Aglaia silvestris,* Family Meliaceae)

Dr. Pattara Sawasdee, Department of Chemistry, Faculty of Science, Chulalongkorn University, studied an active ingredient from 'Chan Chamot' plant to prevent AD by taking its bark to extract and separate the substances in the coumarin group and purify them. Then the test was conducted to test their biological activities compared with the enzyme acetylcholinesterase *in vitro*. It was found that coumarin in 'Chan Chamot' plant could inhibit the enzyme acetylcholinesterase to a certain extent.

4. Research on Using Other MPs for the Treatment of AD

Several scientists from many countries have also conducted research on a few other MPs for the treatment of AD. These are:

4.1 Chinese Clubmoss *(Huperzia serrata,* Family Lycopodiaceae)

Chinese clubmoss, toothed clubmoss, or fir clubmoss is a plant in the group of Lycopodium. It is one of the rarest plants. Prior to this, no scientist had ever tested it in its natural area. A portion of the plant was smuggled out to sell to the Chinese merchants. This new discovery took place on the high mountain at the elevation of 1,000 m in the province of Loem Dong, on the Central Highlands of Vietnam. This plant was once brought for utilization in China several hundred years ago in order to cure inflammation, influenza and abnormality of the blood (Anon. 2008). The recent tests in China demonstrated that it could cure the malfunction of the nervous system, particularly AD. Its extract, huperzine A, first extracted by the Chinese scientists in 1948, received great interest from various western scientists. Such extract is the substance used against the enzyme acetyl-cholinesterase (Anon. 2008).

At present, the (US) National Institute of Aging has done clinical trial in Phase II in order to evaluate the safety and efficiency of said extract in order to use it in the curing of AD patients. In addition, its efficiency in treating epilepsy was tested by scientists from Harvard University (Anon. 2008).

4.2 Snowdrop *(Galanthus nivalis,* Family Amayllidaceae)

This is an MP of the countries of Eastern Europe which has been brought to treat AD since 1950. The active ingredient is galantamine extracted from the bulb of snowdrop. It could inhibit the activities of the enzyme acetylcholinesterase, the neuorotrans-mitter (Cohen 2011).

4.3 Tea *(Camellia sinensis,* Family Theaceae)

The research results used in treating AD in various countries has made tea a medicinal plant (Okello *et al*. 2004). Two groups of scientists have worked on tea:

4.3.1 England: The scientists from the Newcastle University Medicinal Plants Center reported that both green and black teas are able to inhibit the enzyme acetylcholinesterase that destroys acetylcholine, the neurotransmitter. The decrease of this enzyme helps in the

inhibition of the development of AD. In addition, both teas also inhibit the activities of the enzyme butyrylcholinesterase found in the protein plaque attached in the brain of the AD patients. After that Dr. Edwards Okello, Director of the New Castle University Medicinal Plants Center, made additional study to explain how green tea could stimulate our body to protect against AD. He found that after consuming green tea into the body, it is digested in the intestine, creating a chemical effective in inhibiting against the development of AD more than undigested green tea (Okello *et al*. 2004).

4.3.2 USA: The researchers from Southern Florida University reported that green tea could prevent the symptoms similar to AD in the brain of GMO mice which result in having defected brain. The green tea extract, named epigallocatechin-3-gallate (EGCG), is the main antioxidant in the green tea. It was postulated that EGCG reduced amyloid beta, the protein plaque deposited in the brain and led to nerve damage and the loss of memory. The decrease in amyloid beta originated both in *in vitro* cell culture and in the body of the mice. EGCG obstructed from the beginning the process that produced protein plaque causing AD in the brain of the patients. After injecting EGCG for several months into the body of the mice infected with AD, it was found that the deposited substance was reduced by 54% (Rezai-Zadeh *et al*. 2005).

5. Discussion

5.1 From Cause to Discovery

Knowing the cause of disease would lead to the discovery of the active ingredient to cure the disease. In the case of AD, even though at present the scientists still do not know the cause with certainty, there are a number of hypotheses that attempt to explain the cause of AD (Chomchalow 2011). In summary, AD may be the result of the following causes:

- ❖ accumulation of amyloid beta;
- ❖ reduction of acetylcholinesterase; and
- ❖ reduction of estrogen hormone.

Among these causes, some have led to the discovery of MPs which could be utilized in curing AD through the following means:

5.1.1 The Accumulation of Amyloid Beta: The extracts from the root of gardenia, the rhizome of curcuma (Doraiswamy 2009)), and the leaf of green tea (Rezai-Zadeh *et al*. 2005) are effective in destroying amyloid beta and amyloid plaque, which are the possible cause of AD.

5.1.2 The Reduction of Acetylcholine: The extracts from the root of gardenia, the plant of snowflake (Chattipakorn *et al*. 2007), the bark of 'Chan Chamot', the leaf of green tea (Okello *et al*. 2004; Rezai-Zadeh *et al*. 2005), the plant of Chinese clubmoss (Zhu *et al*. 2004) and the bulb of snowdrop (Cohen 2011) have inhibitory effect on the activity of the enzyme acetyl-cholinesterase that digests acetylcholine – the neurotransmitter in the brain.

5.1.3 The Reduction of Estrogen Hormone: Water from young coconut fruit has estrogen enzyme that delays the onset of AD (Radenahmad *et al*. 2011).

However, the researchers of the extracts from 'Prommi' (Boontheuan 2009), black pepper (Chonpathompikunlert *et al*. 2010), and 'Kwao Khreu Khao' (Anon. 2001), that could inhibit the symptoms of AD, did not study the mechanism of how the extracts work.

5.2 From Discovery to Utilization

One of the ultimate goals of doing research is to make use of the results in a practical way. The discovery of active ingredients effective in controlling AD can be utilized in the production of drugs used in AD treatment. So far, three ingredients have been discovered and made use of. These are:

5.2.1 The Utilization of Galantamine from Snowdrop: Galantamine is an alkaloid having inhibitory effect on the enzyme acetylcholine-esterase. Thus it is extracted for use as a drug to cure AD having the trade name of Reminyl (Anon. 2011).

5.2.2 The Utilization of Huperzine A from Chinese Clubmoss: Huperzine A is the substance that counteracts the activity of the enzyme acetycholinesterase. It has chemical structure and process of action similar to the drugs used to cure AD, named galantamine and donepezil. From the clinical trials in China, it was found that huperzine A has the same property similar to the drug used in curing AD

sold in the market and may be safer with respect to side effects (Zhu *et al*. 2004).

5.2.3 The Utilization of Curry Powder from Turmeric: If it is true that curry powder from turmeric is effective in curing AD, there would be development of curry pill which has the same effect as that of curry powder (Doraiswamy 2009). This is a means of cheap protection and treatment in which everyone could reach and could improve the quality of life of a large number of people.

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