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Aegle Marmelos (L.) Correa, A Potential Source for the Treatment of Diabetes Associated Alzheimer's Disease: A Review

Jannat K, Jahan R and Rahmatullah M*

Department of Biotechnology & Genetic Engineering, University of Development Alternative, Bangladesh

***Corresponding author:** Professor Mohammed Rahmatullah, Dean, Faculty of Life Sciences, University of Development Alternative, Lalmatia, Dhaka-1207, Bangladesh, Tel: +88-01715032621; Email: rahamatm@hotmail.com

Review Article

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Abstract

Alzheimer's disease is a chronic neurodegenerative disorder leading to memory loss, which is caused by progressive wasting away of brain cells. Memory loss leads to changes in a person's behavior, thinking and social skills leading in turn to profound alterations in a person's social and family life. The disease can occur by itself with age; however, onset of diabetes can precipitate the onset of the disease or augment the disease process and symptoms. Current allopathic medications can only improve the symptoms of Alzheimer's disease, albeit temporarily and cannot cure the disease. According to the World Health Organization, about 44 million people were suffering from the disease in 2015, a number likely to go up to 114 million by 2050 causing severe strains in family relationships and finances. Plants are a potential source of stopping the development of Alzheimer's or even curing the disease. The present review examines the potential of a plant *Aegle marmelos* or Bengal quince in the treatment of Alzheimer's disease.

Keywords: Alzheimer' disease; *Aegle marmelos;* Bengal quince; Dementia; Diabetes

Introduction

Alzheimer's disease (AD), a chronic neurodegenerative disease is the most common form of dementia characterized by the symptom of short-term memory loss (difficulty in remembering recent events). This condition occurs due to death of brain cells. The disease was first identified and described by a German psychiatrist and neuropathologist Dr. Alois Alzheimer after whom the name was given [1,2]. The prevalence of this disease in contemporary times is in higher progression. An account shows that in 2015 about 44 million of people mostly over 60 years of age were suffering from AD [3]. World Health Organization (WHO) has recently estimated the number of AD patients for 2050 in which the number amplifies to 114 million [4].

Two pathologies are thought to be responsible for the progression of the disease- β-amyloid plaque deposition (build up in the spaces between nerve cells) and

neurofibrillary tangles (build up inside the cells) of hyperphosphorylated tau. β-Amyloid protein is a fragment from an amyloid precursor protein, which in normal brain is broken down but in AD the fragments accumulate to form hard plaques. In normal brains, tau proteins bind to and stabilize microtubules; during AD, tau proteins stick to each other causing the tangles. People generally grow plaque and tangles in their brain during their old age but diagnosis showed that AD patient have a greater tendency to develop these two in their brain. These formations begin in the memory region prior to spread in the others. Scientists believe that development of plaque and tangle has a role on disabling or blocking the communication among nerve cells and they can even damage the process needed for their survival. This disruption of nerve cells causes memory loss, which turns into Alzheimer's disease [5-7]. To understand the etiology of AD, a variety of hypotheses has been made with different degrees of support from epidemiological, clinical and experimental data; these hypotheses include amyloid hypothesis, tau hypothesis, cholinergic hypothesis (deficit of acetylcholine, a neurotransmitter that conduct electrical impulses among nerve cells by rapid hydrolysis by acetyl-cholinesterase); vascular hypothesis (depletion of cerebral blood flow), mitochondrial cascade hypothesis which describes mutations in mitochondrial DNA, oxidative stress, and presence of amyloid b peptide in mitochondria that induces mitochondrial dysfunction and apoptosis of nerve cells leading to AD. Another hypothesis related to metabolic dysfunction or changes in metabolic processes has also been put forth. Diseases like obesity, type 2 diabetes mellitus, hypercholesterolemia also can be cause of Alzheimer's disease [8].

Nowadays, neuropathy is mostly occurring in diabetic patients. Scientists have figured out that there is a connection between these two chronic diseases. The prevalence of this connection is yet to be completely figured out. However, the evidence is increasing of a correlation between diabetes and AD [9-12]. Several studies were done to show the risk factors of developing AD from diabetes. A study was conducted by taking 6,370 elderly people who were under observation for 2.5 years. When the result came out, 126 subjects were found having developed dementia and surprisingly 89 of these were diagnosed with diabetes; notably, increased oxidative stress is a common factor in the pathogenesis of both diseases [13]. People with diabetes are more sensitive to develop AD in their later life. In a recent study researchers have found that there is a relation between growing of amyloid plaque and loss of b cells of islet (insulin producing cells) [14]. Mechanism of diabetes and AD is a riddle; neuroinflammation, oxidative stress [15], amyloid accumulation [16] and mitochondrial dysfunction provoke brain insulin resistance which leads to amyloid b accumulation in brain. Exposure to hyperglycemia and hyperinsulinemia in addition with amyloid b accumulation for a long period causes neuronal deterioration of structure and function [17,18]. Reasons and risk factors are shown in Figure 1.

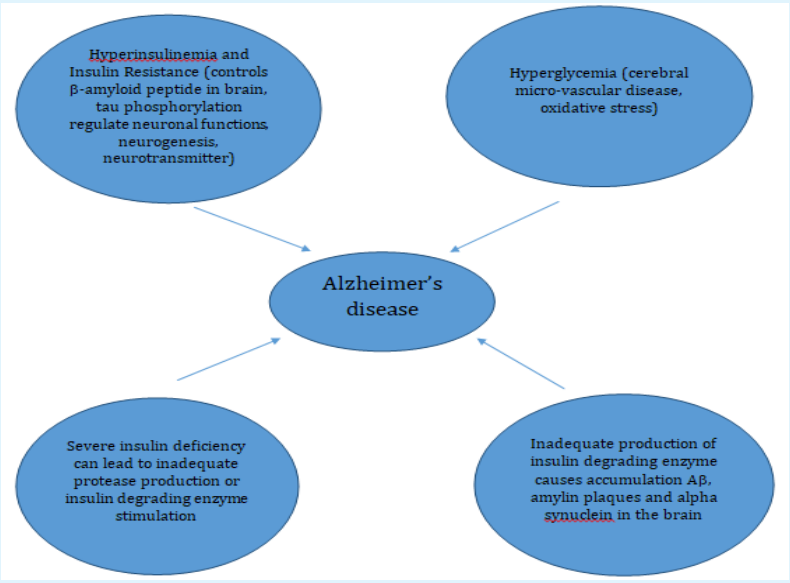

Figure 1: Causes and risk factors of Alzheimer's disease originated by diabetes.

An acceptable theory was established by a recent study which supported the importance of insulin and insulin-like growth factor (IGF-1) in modulating brain function and cognitive process. Insulin enters into the central nervous system through blood brain barrier by a process called saturable receptor mediated process. Insulin transportation becomes slow in AD patient and normally aged person. Location of insulin receptors in the hippocampus, entorhinal cortex, and frontal cortex proves that insulin has a vital role in learning and remembering [19]. This condition (AD) caused by insulin resistance in brain is now often known as type 3 diabetes [20,21].

Currently, AD has no treatment for cure and therefore, the burden of the disease is rising to an epidemic proportion. Various clinical trials have been done already but most of them gave disappointing results [22]. Moreover, the treatments are not cost effective. Natural compounds isolated from plants and animals were investigated against the disease as alternative mode of treatment and found effective for the treatment of AD. Natural extract made from plants are in clinical trials for treatment of different AD conditions (mild to moderate, severe, severe AD, vascular dementia etc.); the various plants or plant products tested include *Ginkgo biloba*, saffron, coconut, green tea, lemon balm, sage, blueberry and some others [23]. *Aegle marmelos* (L.) Correa commonly known as bael (in Bengali) and Bengal quince or goilden apple (in English) has been used in Ayurveda and folk medicine of Bangladesh for over 500 years for the treatment of various diseases comprising diabetes and memory loss [24]. The plant has been used for retrieving memory or enhancing the capability of remembering that was deteriorated because of diabetes. The rest of the review will focus on the pharmacological properties and phytochemicals present in the plant and discuss the potential of the plant or its various parts in the treatment of diabetes-induced AD.

Aegle marmelos (L.) Correa

Aegle marmelos is a moderate sized (6-8m), slender, aromatic tree of Rutaceae family. The plant is indigenous in Southeast Asian countries. It is commonly known as bael in Bengali. Almost all parts of the plant are used for medicinal purposes like stem, bark, fruit, leaf, seed, seed oil, root, flower etc. Bael is considered as a holy plant among the Hindu community [25,26].

Phytochemicals

Chemicals present in different plant parts are mainly secondary metabolites. Medicinal properties of plant are usually regulated and specified by these chemicals. Secondary metabolites not only give a plant the capability of curing disease, it provides a defense against various external threats [27,28]. Alkaloids, tannins, coumarins, steroids, polysaccharides, carotenoids have been isolated from individual parts of the plant (*Aegle marmelos*). *Aegle marmelos* leaves are rich in g-sitosterol, aegelin, lupeol, rutin, marmesinin, b-sitosterol, flavone, glycoside, *O*-isopentenylhalfordiol, marmelin, and phenylethyl cinnamamides [29]. Various phytochemicals present in *Aegle marmelos* are shown in Table 1.

Alkaloids	Plant parts	References
O-3,3-(dimethylallyl)halfordinol	Leaf	[30]
N-2-ethoxy-2-(4-methoxyphenyl) ethylcinnamamide	Leaf	[30]
N-2-methoxy-2-[4-(3',3'-dimethylallyloxy)phenyl] ethylcinnamamide	Leaf	[30]
N-2-methoxy-2-(4-methoxyphenyl) ethylcinnamamide	Leaf	[30]
N-2-hydroxy-2-[4-(3',3'-dimethylallyloxy)phenyl] ethylcinnamide or marmeline	Leaf	[30]
N-4-methoxystyryl cinnamide	Leaf	[30]
N-2-hydroxy-2-(4-hydroxyphenyl) ethylcinnamide	Leaf	[30]
Anhydromarmeline	Leaf	[29,30]
Aegelinosides A	Leaf	[29,30]
Aegelinosides B	Leaf	[29,30]
marmelos	Dry Leaf	[30]
N-2-hydroxy-2-(4-methoxyphenyl)-ethylcinnamamide (aegeline)	Leaf, root	[30]
4,7,8-trimethoxy-furoquinoline (skimmianine)	Leaf, root	[30]
N-2-ethoxy-2-ethyl cinnamid	Leaf	[31,32]
Aeglenine	Leaf	[31,32]

Terpenoids		
Terpenoids	**Plant parts**	**References**
Lupeol	Root bark	[32]
a-Phellandrene	Leaf oil	[30,31,47]
p-Cymene	Leaf oil	[30,31]
p-Menth-1-en-3,5-diol	Leaf	[30,31,33]
Limonene	Leaf	[30,31,33]
g-Sitosterol	Leaf	[30,31]
a & b-Amyrin	Leaf, stem bark, root, fruit	[30,31]
b-Sitosterol	Leaf, stem bark, root, fruit	[30,31]
a- Pinene	Leaf, twig, fruit	[33]
b-Myrcene	Whole plant	[31]
b-Ocimene	Whole plant	[31]
d- Carene	Whole plant	[31]
Isosylvestrene	Whole plant	[31]
Flavonoids		
Chemicals	**Plant parts**	**References**
Rutin	Leaf	[31]
Flavon-3-ol	Whole plant	[31]
Flavon glycosides	Whole plant	[31]
Coumarins		
Coumarins	**Plant parts**	**References**
Psoralen	Root	[32,33,47]
Xanthotoxin	Root, root bark	[32]
Dimethoxycoumarin	Root	[32]
Scopoletin	Root	[32,33,47]
Urbelliferone	Root, root bark	[33,34]
Marmesin	Root, root bark	[31,32,47]
Marmin	Root	[32,33,47]
Skimmin	Root	[32]
Imperatorin	Whole plant	[31]
Marmelide	Whole plant	[31]
Alloimperatorin	Whole plant	[33]
Essential oils		
Chemicals	**Plant part**	**References**
a- Pinene	Leaf	[34,35]
b- Myrcene	Leaf	[34]
a- Phellandrene	Leaf	[34,35]
Isosylvestrine	Leaf	[34]
d- Careen	Leaf	[34]
b-Ocimene	Leaf	[34,35]
trans-2-hydroxycinnmic acid	Leaf	[34]
Terpenolene	Leaf	[34]
Linalool	Leaf	[34]
3-isothujanol	Leaf	[34]
4-Terpineol	Leaf	[34]
a -Terpineol	Leaf	[34]
Thuj-3-en-10-al	Leaf	[34]
d & g-Elemene	Leaf	[34]
a -Cubebene	Leaf	[34]

Valencene	Leaf	[34]
b-Selinene	Leaf	[34]
a-Duprezianene	Leaf	[35]
Caryophylline	Leaf	[35]
b-Elemene	Leaf	[35]
Germacrene	Leaf	[35]
(3Z)-Hexenylhexanoate	Leaf	[35]
iso-3-Thujanyl acetate	Leaf	[35]
β-Atlantol	Leaf	[35]
Miscellaneous compounds		
Chemicals	**Plant parts**	**References**
Praealtin D	Leaf	[30]
trans-cinnamic acid	Leaf	[30]
4-methoxybenzoic acid	Leaf	[30]
N-p-cis-& trans-coumaroyltyramine	Leaf	[30]
montanine, rutaretin	Leaf	[30]

Table 1: Phytochemicals reported in *Aegle marmelos*.

Ethnomedicinal Use of Bael in Enhancing Memory and Treatment of Diabetes

In Ayurvedic treatment of neuropathy *Aegle marmelos* fruits have been in use to enhance memory for over 1500 years. Among folk medicine practitioners of Bangladesh, this plant is quite popular as a memory enhancer [36]. Bangladesh folk medicine practitioner use the plant leaves to increase memory. Leaves are fried in a little ghee (clarified butter) and advised to take orally with honey to increase memory [37].

Aegle marmelos is a well-known medicinal plant among Ayurveda and Siddha system for the treatment of diabetes. Its leaves are highly antidiabetic [38]. The Loi community of Manipur, Northeast India eats tender raw leaves with milk to treat diabetes [39]. Indigenous people of Nalbari district, Assam take the leaf powder with cow's milk daily in order to cure diabetes [40]. Decoction made from leaves is orally taken on an empty stomach every morning in Nepal [41]. The poor people of Kerala also use bael leaves to treat diabetes. They grind the leaves, make it into small pills and orally take once a week [42]. A combination three plant parts work as antidiabetic. Powder of leaves of *Aegle marmelos*, seed powder of *Azadirachta indica* and *Syzygium cumini* are mixed together with water which is then orally taken twice a day [43]. Folk medicine practitioners as well as native people of Bangladesh use this plant for the treatment of diabetes. Leaf juice is drunk by the people of Brahmanbaria district [44]. A tradition of chewing and swallowing leaves of bael every morning is very common among the Paliyars tribe, Tamil Nadu, India [45]. Drug obtained by distillation of flowers is used for the treatment of diabetes [46].

Pharmacological Evidence

Aegle marmelos is a potential alternate to treat Alzheimer's disease or to enhance remembering capability [47]. A number of investigations have been done already. Mice, that were given different doses (100, 200, 400 mg/kg oral) of methanolic leaf extract of bael fruits showed significant progress of remembering as examined through Morris Water Maze method and Pole Climbing test. Mice were at first treated with scopolamine to induce memory impairment [48]. Another experiment was designed with Wistar Albino rats. They were administered ethanolic extract of leaf at the doses of 200 and 400 mg/kg for 14 days; streptozotocin (3mg/kg) was injected to rats on 1st and 3rd day of the experiment. After three weeks of administering streptozotocin, biochemical and histopathological studies were carried out, which revealed increase in level of oxidative stress marker malondialdehyde, nitrite, acetylcholinesterase activity (indicates cholinergic hypofunction and neuronal damage) and decrease in glutathione level. All these were ameliorated by extract of bael leaf which proved the tree has therapeutic value in treating AD [36, 49].

Acetylcholinesterase inhibition and antioxidant properties were checked with methanolic extract of leaf and four solvent fractions of petroleum ether, chloroform, ethyl acetate and water. Among them ethyl acetate fraction gave an outstanding result in acetylcholinesterase inhibition activity performed by

Ellman method and reducing oxidation; the fraction also demonstrated radical scavenging activity of 1,1-diphenyl-2-picrylhydrazyl and inhibited lipid peroxidation in brain as well. The fraction was a rich source of polyphenolic compounds, which were considered responsible for showing all these activities and hence considered to be helpful for the treatment of Alzheimer's disease [50,51].

To evaluate anti-amnesic activity of *Aegle marmelos*, leaves were taken and extracted with ethanol. Adult male albino rats were exposed to electroshock (MES) and scopolamine to produce loss of memory. Chronic exposure resulted in significant decrease and increase in latency time measured by step down latency and transfer latency in elevated maze respectively. Scopolamine exposure showed increase in acetylcholinesterase activity. By treating with ethanol extract of leaf all these symptoms were ameliorated significantly ($P<0.01$) [52]. It was stated before that every part of the plant possess therapeutic value. Not only leaves of this plant are used to treat AD, but also fruits and seeds are used. Methanolic extract of fruits showed nootropic effect that was tested on three groups of Wistar Albino rats by Morris water maze. Both the scopolamine treated and without scopolamine group showed significant increase in memory [53]. Dried fruit extracts (doses 200mg/kg and 400mg/kg) also showed effective result against cognitive defects mainly Alzheimer's disease [54]. A comparison of nootropic effect was shown between *Aegle marmelos* extract and standard drug Piracetum. An experiment was conducted by taking male Wistar rats divided into four groups, each group comprised of six rats. Group two, three and four were treated with extract at 100 mg/kg, 200 mg/kg and 200 mg/kg, respectively, for seven consecutive days. Assessing learning and memory by elevated plus maze method showed that both doses showed significant decrease in transfer latency from 6th day to 7th day ($p<0.05$) [55].

Beneficial effects on AD or causes like diabetes leading to AD can be obtained individually or in combination through treatment of memory loss, diabetes, and oxidative stress. *Aegle marmelos* can be a treatment of diabetes as well [56]. There are plenty of evidences that support this statement. Antidiabetic effects of the plant and plant parts as well as any reported responsible phytochemicals are shown in Table 2.

Extract or active compound	Experiment model	Effect on diabetes	Reference
Hydroalcoholic extract of roots	Alloxan-induced diabetic mice	Significantly ($P<0.05$) lessened blood glucose level.	[57]
Aegeline (N-acylated-1-amino-2- alcohol) from leaves	*In-vitro*	Increased insulin sensitivity by activation of b3-AR pathway. (AR stands for adrenergic receptor)	[58]
Extract of fruits and leaves	Streptozotocin (90mg/kg) induced diabetic Long Evans Rats	Lowered insulin resistance.	[59]
Leaf extract	Streptozotocin (90mg/kg) induced diabetic Long Evans Rats	Significantly ($P<0.05$) increased insulin secretion, a-amylase and intestinal disaccharidase enzyme activities, reduced glucose absorption.	[60]
Aegeline (N-acylated-1-amino-2- alcohol) from leaves	*In-vitro*	Increased peripheral insulin sensitivity by stimulating PI3-kinase-Rac1-PAK1-cofilin pathway which was mediated by two distinct but parallel pathways Akt and Rac1 to stimulate glucose transporter.	[61]
Umbelliferone β-D-galactopyranoside from stem bark	Streptozotocin (60mg/kg) induced Swiss Albino Wistar rats	Increased level of pancreatic insulin secretion and antioxidant activity.	[62]
Methanolic extract of bark	Streptozotocin (60mg/kg) induced male Swiss Albino Wister rats	Significantly reduced blood glucose level, increased regeneration of pancreatic b cells.	[63]
Methanolic extract of leaves	*In-vitro*	Inhibited a-amylase activity.	[64]
Ethanolic extract of leaves	Streptozotocin (55mg/kg) induced male Swiss Albino Wistar rats	Initialized regeneration of Islet cells and increase in the islet cells compared to the diseased pancreas.	[65]
Umbelliferone (7-	Streptozotocin	Improved glycemic control resulting in reduced	[66]

hydroxycoumarin) from fruits	(40mg/kg) induced Swiss Albino Wistar rats	formation of circulatory and tissue glycoprotein components.	
Aegeline 2 from leaves	Streptozotocin (100mg/kg) induced Swiss Albino Wistar rats	Significantly decreased blood glucose level, may have activity as b3-AR agonist.	[67]
Aqueous extract of seeds	Diabetic rats	Increased glucose tolerance.	[68]
Aqueous extract of leaves	Alloxan induced diabetic rats	Lowered blood glucose level, decreased glutathione-S-transferase and malondialdehyde, increase in glutathione which indicates hypoglycemic and antioxidant activity.	[69]
Aqueous extract of fruits	Streptozotocin (45mg/kg) induced diabetes in female Swiss Albino Wistar rats	Decreased plasma insulin level.	[70]
Anhydroageline	*In- vitro*	Inhibitory effect against a-glucosidase.	[71]

Table 2: Antidiabetic effects of the plant along with any reported responsible phytochemical.

Concurrent epidemiological studies strongly supports that diabetes remarkably increases the risk of developing AD. In addition, both insulin and insulin like growth factor 1 (IGF-1) have been found in reduced amount in the brain of AD patients and most of the patients developed diabetes or glucose intolerance [72,73]. Different antidiabetic compounds have already been investigated against AD which revealed significantly beneficial results [74]. In a study done by Vandal et al., they genetically induced AD-like neuropathology in mouse fed with high fat diet, which led to peripheral glucose intolerance with pancreatic human Aβ (amyloid beta) accumulation, enhanced brain soluble Aβ, and memory impairment in 3xTg-AD mice. But a single dose of insulin injection reverted the effect of high fat diet and reduced the amount of brain soluble Aβ and enhanced memory [75]. Treating APPSWE/PS1dE9 mice with an analogue Liraglutide (glucagon like peptide 1) that was approved for the treatment of type II diabetes, significantly lessened IRS-1pS (616) that is the insulin receptor substrate (IRS)-1 phosphorylated at serine 616. It also decreased the amount of amyloid plaque formation and glia cells associated to amyloid loads [76]. Cognitive function was improved by inhibiting cyclin-dependent kinase 5 (cdk 5) activities by treating APPSWE/PS1dE9 mice with pioglitazone (10mg/kg) [77]. Another antidiabetic drug lixisenatide restored cognitive and synaptic function when it was given to APPSWE/PS1dE9 mice by reducing Ab pathology [78].

Considering the beneficial nootropic effect of antidiabetic agents and as *Aegle marmelos* has antidiabetic properties, it can be stated that this plant has the potency to treat AD in diabetic patients. Aqueous extract of seeds of *Aegle marmelos* was administered to streptozotocin induced diabetic Wistar rats at doses of 100, 250 and 500 mg/kg. A sharp improvement of spatial learning and memory was noticed between control and treated mice. Swimming time or escape latency was significantly lower ($P<0.01$) in extract treated groups than control; on the other hand swimming speed was remarkably higher ($P<0.05$) than control in *Aegle marmelos* extract treated groups [79-81].

Conclusion

Overall, the results quite conclusively suggest that antidiabetic drugs can have beneficial effects on diabetes-induced AD. Diabetes can lead to AD in multiple ways as shown in Figure 1. At the same time, oxidative stress is both a consequence and a factor leading to diabetes. Thus the solution to diabetes-induced AD might lie in a drug which combines memory enhancing, antidiabetic and antioxidant properties.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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